ON THE CONSTITUTION OF DISUBSTITUTED ISOTHIOHYDANTOINS :

by

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A Thesis Submitted to the Department of Chemistry
and to the Faculty of the Graduate School
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of

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- 1929 -

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This thesis is dedicated to my wife Monna D. Long, whose sacrifice, encouragment and cooperation made it possible.

CONTENTS

I N T R O D U C T I O N

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I. Primary Aromatic Amines react with Chloracetyl Chloride to form Chloracetarylamides:- (Beckurts and Frerichs.)[1]

$$Ph \cdot NH_2 + Cl \cdot CO \cdot CH_2 \cdot Cl = Ph \cdot NH \cdot CO \cdot CH_2 \cdot Cl + HCl.$$

II. Chloracetarylamides react with Potassium Thiocyanate to form Thiocyanacetarylamides:- (Beckurts and Frerichs.)

$$Ph \cdot NH \cdot CO \cdot CH_2 \cdot Cl + K\ S\ CN = Ph \cdot NH \cdot CO \cdot CH_2 \cdot S \cdot CN + K\ Cl.$$

III. Thiocyanacetarylamides rearrange to Arylthiohydantoins:- (Beckurts and Frerichs.)

$$Ph \cdot NH \cdot CO \cdot CH_2 \cdot S \cdot CN = \begin{array}{l} Ph\ N \text{———} CO \\ \quad\ | \qquad\quad | \\ HN = C \quad\ CH_2 \\ \qquad \diagdown S \diagup \end{array}$$

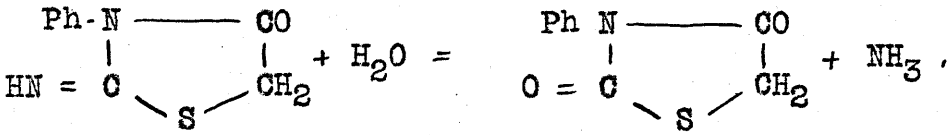
IV. These Arylthiohydantoins form salts with Sodium Hydroxide, which crystallize with a number of moles of water:- (Beckurts and Frerichs.)

$$\begin{array}{l} Ph \cdot N \text{———} CO \\ \quad\ | \qquad\quad | \\ HN = C \quad\ CH_2 \\ \qquad \diagdown S \diagup \end{array} + NaOH + XH_2O = \begin{array}{l} Ph \cdot N \text{———} CO \\ \quad\ | \qquad\quad | \\ H\text{-}N = C \quad\ CH_2 \\ ONa \diagup \qquad \diagdown S \diagup \\ \quad H \end{array} .XH_2O.$$

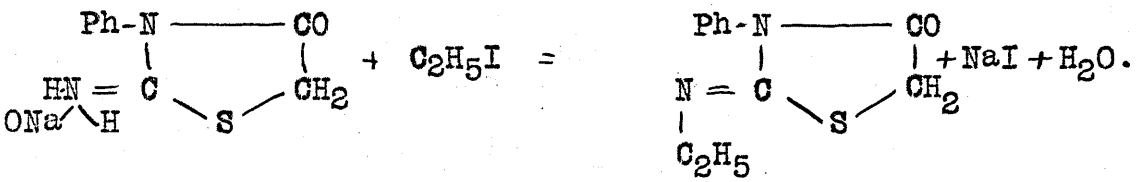
V. These Arylthiohydantoins(III) on hydrolysis with

(1) Archiv. d. Pharm. 253, 233-65 (1915).

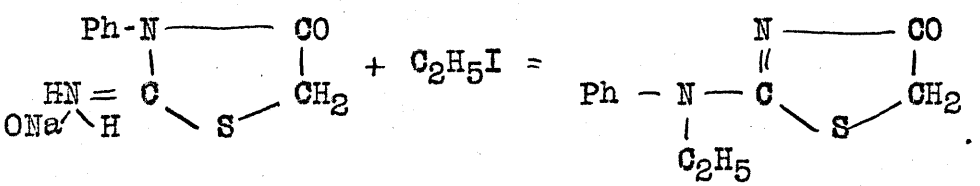
strong HCl-solution yield Arylmustard Oil Glycolides by replacement of the HN= -group with oxygen:- (Beckurts and Frerichs.)



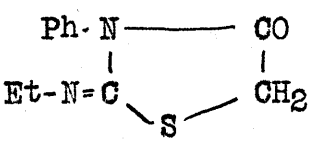
VI. The salts, (IV), with Ethyl Iodide, yield, (according to Beckurts and Frerichs), γ- Ethyl -β- Aryl-thiohydantoins,



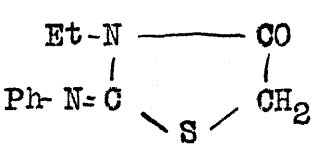
VII. The salts (IV) with Ethyl Iodide, according to this investigation, produce γ, γ-Ethyl-Aryl-thiohydantoins,



and in some cases there is produced together with the γ,γ- product an γ, β- product,



or, possibly,

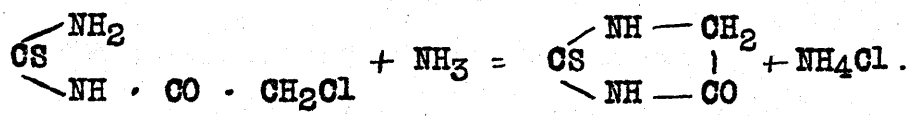


H I S T O R I C A L

Richard Maly[1], in May, 1873, obtained thiohydantoin from chloracetylthiourea. His statement in regard to its formation follows:

"Aus diesem Chloracetylsulfoharnstoff erhält man leicht das Hydantoin aus der Reihe der geschwefelten Harnstoffe, das sich von dem von Baeyer[2] entdeckten Hydantoin (Glycolylharnstoff) nur dadurch unterscheidet, dass es statt 1 O ein Atom S enthalt, und daher Glycolylsulfoharnstoff oder Sulfhydantoin genannt werden kann."

For the reaction involved he writes:



J. Volhardt[3], in March, 1773, notice of the above mentioned work of Maly having come to his attention ("Im Anzeiger der k. Akad. d. W. zu Wien 1873, Nr. 6.") states: "Ich war mit dem gleichen Gegenstand beschäftigt und hatte den Glycolylsulfoharnstoff bereits in Händen, als ich von obiger Notiz Kenntniss erhielt." --- "Ich

(1) Maly: Ann. Chem. Pharm. 168, 133.
(2) Baeyer: " " " 130, 129.
(3) Volhardt: " " " 166, 383.

denke nicht daran, Maly die Entdekung des Glycolylsulfoharnstoffs streitig zu machen: anderseits halte ich mich um so mehr für berechtigt, meine unabhängig von Maly begonnene Untersuchung fortzusetzen, als ich dieselbe hauptsächlich zum Zweck des Studiums der Entschwefelungsproducts dieser Körper begonnen habe." He refers again to this product in a later publication(1), and demonstrates that thioacetic acid (Senfölessigsäure) is a product of its hydrolysis:

$$\begin{matrix} CH_2 - NH \\ | \quad\quad | \\ CO - NH \end{matrix} \!\!\diagdown\!\!\diagup CS + HCl + H_2O = H_4NCl + \begin{matrix} CH_2 \cdot NCS \\ | \\ CO \cdot OH \end{matrix}$$

M. Nencki(2), in May, 1873, refers to the above publication and remarks:

"Unabhängig von Maly und Volhardt habe ich ebenfalls den chloracetylsulfoharnstoff dargestellt und analysirt. Erst nachdem ich die Kenntniss von der Maly'schen Entdeckung erhalten, habe ich die weitere Untersuchung dieses Körpers aufgegeben."

E. Mulder(3) (October, 1875) obtained thiohydantoin by the action of chloracetic ester on thiourea and also from monochloracetamide and the urea:

I.
$$CH_2 \cdot Cl \cdot CO \cdot C_2 H_5 \text{ --- } O + NH_2 \cdot CS \cdot NH_2 = HCl + C_2H_5 \cdot HO + CS \begin{matrix} NH - CH_2 \\ | \quad\quad | \\ NH - CO \end{matrix}$$

(1)Volhardt: J. f. Prak. Chem. 1874, (2), 6.
(2)Ber. VI. 599.
(3)Mulder; Ber VIII, 1264.

II $CH_2 \cdot Cl \cdot CO \cdot NH_2 + NH_2 \cdot CSNH_2$

$= ClH + NH_3 + CS\begin{matrix} NH - CH_2 \\ NH - CO \end{matrix}$,

Peter Claesson(1), in March, 1876, prepared it from thiourea and chloracetic ester in alcholic solution, however as a byproduct in his work on thioacetic acid (Senfölessigsäure).

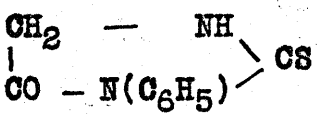
Paul J. Meyer(2), in 1877, mentions the work of these authors and observes that the presence of two ammonia residues in the thiohydantoin ring which are differently placed in respect to the glycolyl grouping renders possible the existance of two series of isomeric compounds, according as substitution takes place on the nitrogen next to carbonyl or on that next the methylene grouping, as shown in the following picture:

$CH_2 \cdot \boxed{Cl \quad H} NH \diagdown CS$ and $CH_2 \cdot \boxed{Cl \quad H} \cdot NH \diagdown C=S$

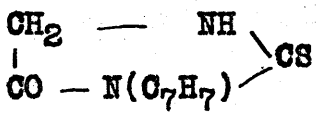
$CO \boxed{NHC_6H_5 \quad H} NH \diagup$ $CO \cdot N \cdot C_6H_4 \cdot \boxed{H \quad HNH} \diagup$.

He attempts the preparation of representatives of the first class and succeeds in making mono-phenyl- and mono-tolyl-thiohydantoin by the action of thiourea on the chloracet derivatives of the amines. To these he assigns the following structure, though at this time presenting no experimental proof for the selection:

(1) Claesson: Ber X, 1352.
(2) Meyer: Ber 10, 1965 (1877).

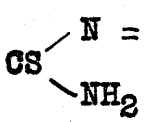


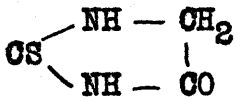
m.p. 178°



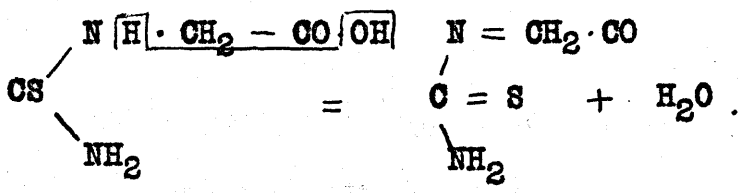
m.p. 183°

In both cases he obtained also the unsubstituted thiohydantoin. (m.p. 200+°).

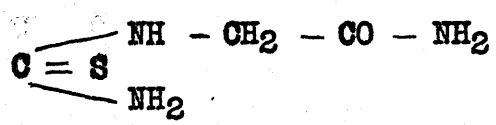
He adds that the existance and mode of formation of these bodies can with difficulty be harmonized with the theory of Maly[1] concerning the constitution of the thiohydantoins. The latter had proposed the following structure for thiohydantoin,  , on the theory that it accounts for the basic properties of the compound in a way not shown by the structure:



and that it accounts well for its formation from thiohydantoic acid:



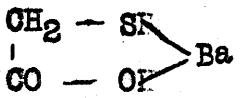
He reasoned also that thiourea and monochloracetamide should give the compound:



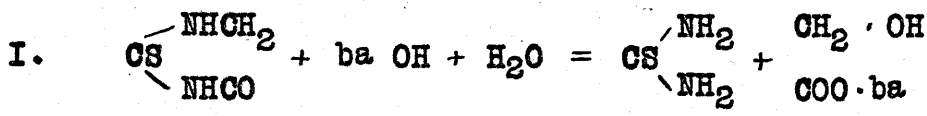
but adds: "Das Amid ist also auf diese Art nicht zu gewinnen."

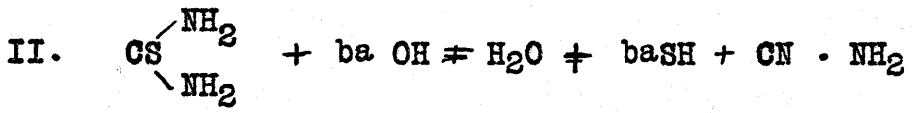
(1) Maly: Ber 10, 1853 (1877).

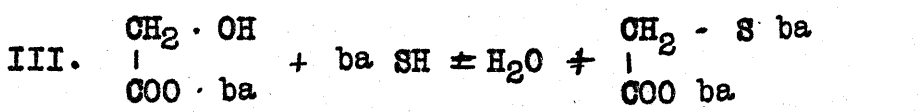
Rudolf Andreasch[1], by treating thiohydantoin with baryta water, obtained the barium salt of thioglycollic acid,



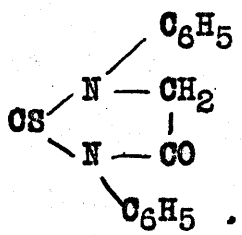
He pictures the reactions involved as follows:







A. Lange[2] prepared diphenyl thiohydantoin by treating diphenylthiourea with monochloracetic acid in alcoholic solution. His picture of the product follows:



Heated in alcoholic potassium hydroxide for some time he claimed it decomposed as follows:

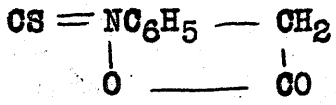
$C_{15}H_{12}N_2SO + 3KHO = C_{13}H_{12}N_2O + K_2S + C_2H_3KO_3$

while with dilute hydrochloric acid the reaction was as follows:

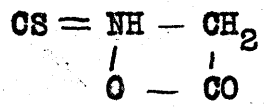
$C_{15}H_{12}N_2SO + HCl + H_2O = C_9H_7N\,SO_2 + C_6H_7NHCl$.

He favored the following structure for the product of acid hydrolysis:

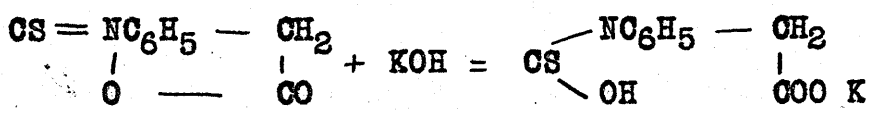
(1) Ber XII, 1385, (1879).
(2) " " 1588, (1879).



and suggests for the hydrolytic product of the unsubstituted thiohydantoin an analogous structure:

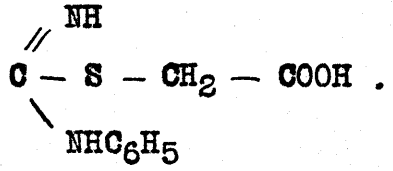


and for the action of KOH :



C. Liebermann and A. Lange[1] investigate further these products of Lange and state that their work throws new light on the constitution of thiohydantoin. They find that by the action of potassium hydroxide on diphenylthiohydantoin, not glycollic acid ($C_2H_4O_3$) but thioglycollic acid, $CH_2 - SH$, $COOH$, is produced.

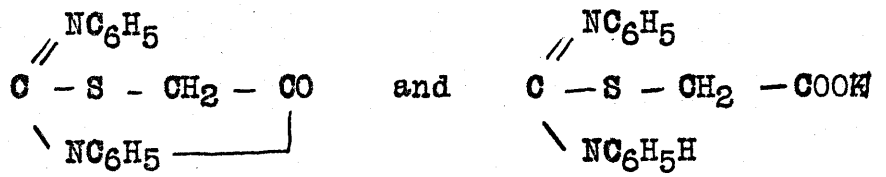
Jager[2] had in Nencki's laboratory obtained from ammonium thiocyanate, aniline and monochloracetic acid, a compound, $C_9H_{10}N_2SO_2$, which they called phenylcarbodiimidosulfoacetic acid and to which they attributed the structure



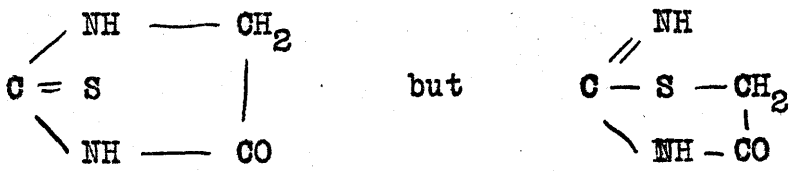
on the grounds that on treatment with dilute acids it broke up into monophenylthiourea and thioglycollic acid. It thus showed an analogous decomposition to that of diphenylthiohydantoin with potassium hydroxide.

(1) Ber XII. 1588, (1879).
(2) Jr. f. pr. Chem (2) 16, S. 17.

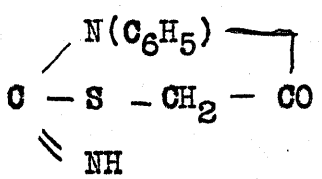
He suggests for Jager's product the name monophenylthiohydantoic acid as being more suitable. In view of these results they adopt the following structures for diphenylthiohydantoin and the corresponding acid:



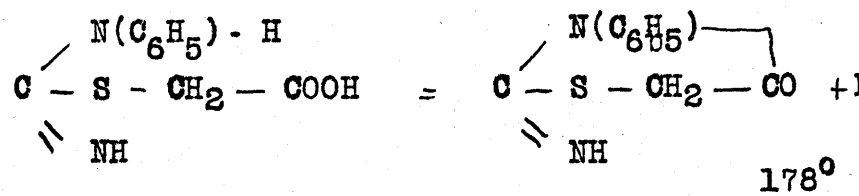
They conclude that the new conception of the constitution of diphenylthiohydantoin must be carried over to all other thiohydantoins: that the simplest thiohydantoin is not as heretofore named:



P. Meyer[1], calling attention to this work of Liebermann and Lange, states that to the phenylthiohydantoin obtained by him, hereafter, was due in virtue of its mode of formation, the structure:

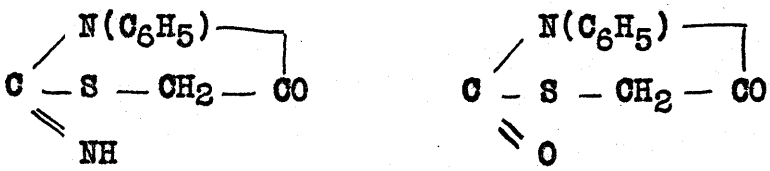


He prepared some of the compound from phenylthiohydantoic acid by heating it with glacial acetic acid for a short time.



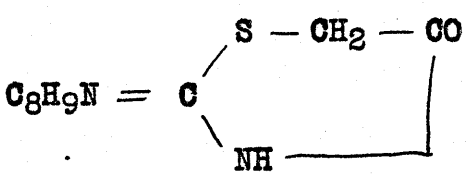
(1) Ber 14, 1661, (1881).

He found that when heated with dilute hydrochloric acid until a sample removed solidified on a watchglass, the solution, on cooling, deposits a solid, melting at 148°. Analysis of this shows it to be Lange's phenylmustard oil glycolide.



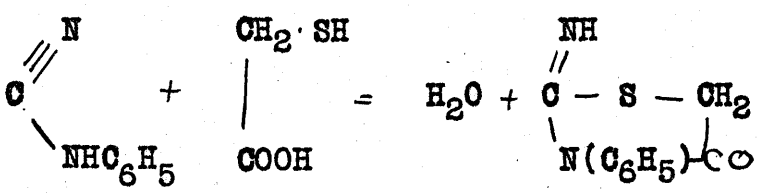
m.p. 148°

Alfred Neubert[1] prepared monophenylethylthiohydantoin from monophenylethylthiourea and monochloracetic acid in alcoholic solution. The following structure was assigned to it by him:



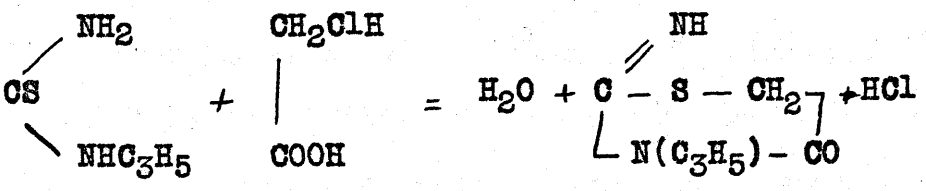
though he offered no experimental evidence for his selection.

Andreasch[2] prepared phenylthiohydantoin from phenylcyanamide and thioglycollic acid:

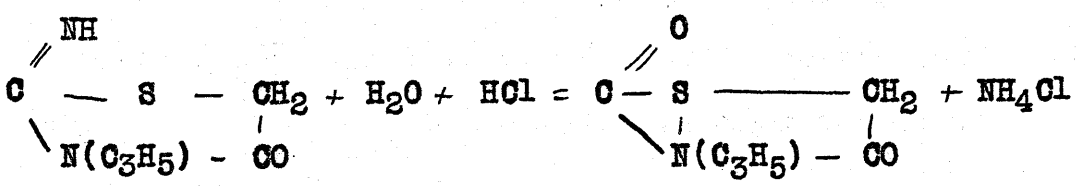


and allylthiohydantoin from chloracetic acid and allylthiourea:

(1) Nembert: Ber. 19, 1823, (1886).
(2) Andreasch: Ber. 15, 326, (1882).

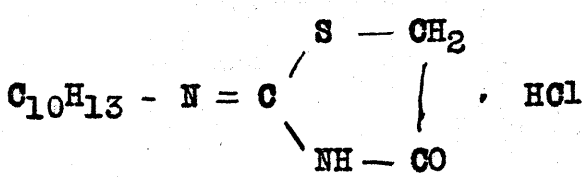


The above compound on recrystallization or by heating for some time undergoes change as follows:



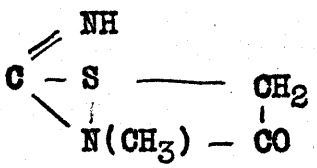
basing his conclusion largely on the fact that, beside the oily diketo derivative, he obtained only ammonium chloride and none of the allylamine which should have been obtained in case the isomer were present.

Heinrich Goldschmidt and Victor Badl[1] prepared the HCl salt of Cumenylthiohydantoin by warming an alcoholic solution of Cumenylthiourea and monochloracetic acid. They assigned to the compound the structure:



though offering no experimental evidence for it.

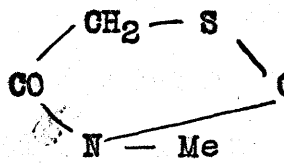
It appears that Andreasch worked with methylthiohydantoin[2] and assigned to it according to Dixon[3], [but this volume of the Journal was not available],



(1) Goldschmidt: Ber. 22, 933 (1889).
(2) Andreasch: Monats., 6, 842, (1885).
(3) Dixon: Jr. Chem. Soc. (London) 71, 619, (1897).

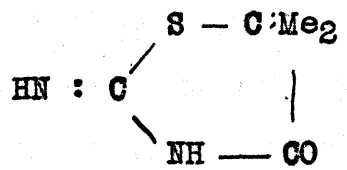
From these considerations it appears that investigators at this time were not agreed as to the position of the radicles where substitution occurs at a single nitrogen atom.

Andreasch[1] prepared nitrosothiohydantoin and found on hydrolysis that it produced hydroxylamine among the products. He also made methylthiohydantoin



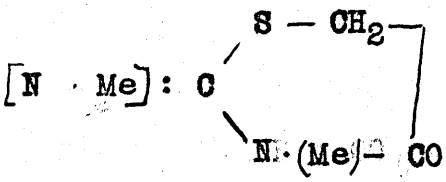
m.p. 114°, from "methyl thiocarbamide and chloracetic acid." Nitrous acid converts it into isonitrosomethylthiohydantoin. With baryta water this gives the barium salt of isomitrosomethylthioglycollic acid.

Two years later[2] he prepared the disilver salt of thiohydantoin which with methyl iodide he claimed gave B-dimethylthiohydantoin,



m.p. 114°.

He prepared the isomer γ,β-dimethylthiohydantoin



m.p. 71°.

from dimethylcarbamide and chloracetic acid.

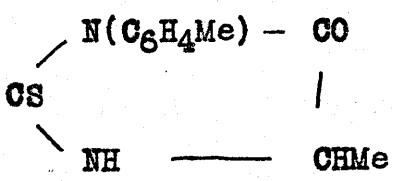
Thiohydantoin, he found to react with benzaldehyde to produce the benzal derivative of the acid,

NH : C(NH2) COOH : CH Ph.

(1) Chem. Abs. Jr. Chem. Soc. (London)(1892):(Monatsh. Chem. 6. 821 - 843 (1891).
(2) Monatsh. 8, 407 - 424.

Markwald, Neumark and Stilzner[1] in a contribution entitled "Hydantoins and Bases Derived from Them", say, in part, "Hydantoins have been known hitherto only in the aromatic series, having been obtained (Aschen. Abstr. 1884, 907) be melting together aromatic thiocarbamides and amido acids of the fatty series." They prepared and described a large number of derivatives containing an aryl group, and gave to them the structure of the true thiohydantoins. As an example,

O - tolylmethylthiohydantoin,



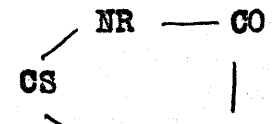
m.p. 198°

is given here. It is prepared from o-tolylmethyl-thiocarbamide and alanine.

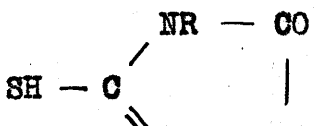
The authors consider these compounds to represent a new type of thiohydantoin. They say that all show the characteristic properties of thiocarbamides. They yield insoluble silver and mercury salts which readily decompose, forming metallic sulphides. They dissolve in alkalies and when the solutions are boiled, salts of the corresponding thiohydantoic acids are formed. But as the first result of the action of alkali, compounds of another nature are formed, which have not been isolated, but derivatives of which have been prepared.

(1) Ber. 24, 3278,-3298, (1891).

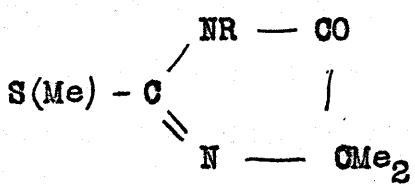
Take as an example the methylthiohydantoins derived from alanine. With potash they react according to the formula,



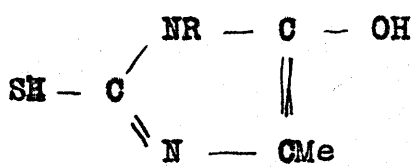
, yielding salts of methylthiohydantoic acid. But if they are dissolved in potash and methyl iodide is added, they react according to the formula,



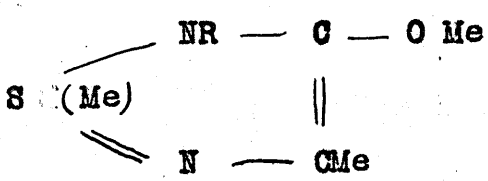
, and take up two methyl groups. This may give



an imidazolone, or the thiohydantoin may react in yet another form,



, of the second of the two formulas given above, yielding

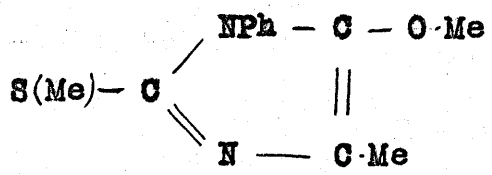


an imidazole. In reality the compound formed has the last formula --------."

The methylthiohydantoins derived from alanine react with two moles each of potash and methyl iodide

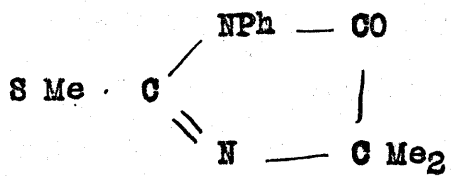
in alcoholic solution. Typical of these is

ν-phenyl-γ-methoxy-β-methyl-μ-thiomethylimidazole,



m.p. 90°.

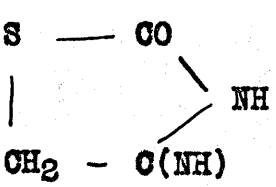
Imidazolones were prepared by treating the dimethyl-hydantoins derived from γ-amidoisobutyric acid, with one mole each of potash and methyl iodide in alcoholic solution.



m.p. 222-225°.

ν-phenyl-B-dimethyl-μ-thiomethylimidazolone.

Miolati[1] prepared thiocyanacetamide, $NH_2 \cdot CO \cdot CH_2 \cdot SCN$, by heating chloracetamide with potassium, ammonium or barium thiocyanate in alcoholic solution, m.p. 112°. By dissolving this compound in dilute sulphuric acid and after 24 hours extracting with ether, he obtained isothiohydantoin, m.p. 71°.



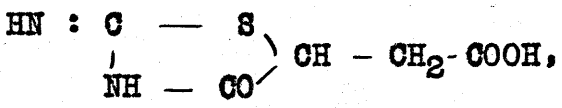
Prolonged action of acids converts it into dioxythiazole.

C. Matignon[2] finds the heat of combustion of

(1) Abs. J. Chem. Soc. (London) 1893: Gazzetta, 23 i, 90-95.
(2) Ann. Chem. Phys. (6), 289-394.

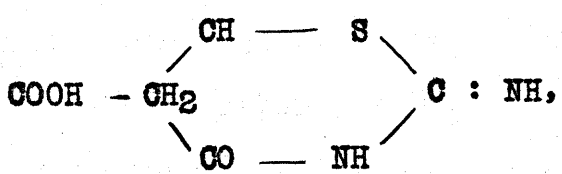
thiohydantoin at constant volume to be +502 Calories and that at constant pressure, +58.9 Calories.

R. Tambach[1] obtained thiohydantoic acid,



by warming a mixture of thiocarbamide with bromosuccinic acid in molecular proportions. It decomposes without fusion at 210°. By heating together alcoholic solutions of diphenylthiocarbamide and bromosuccinic acid or by fusion, he obtains diphenylthiohydantoinacetic acid. The dioxythiazoleacetic acids are obtained from these by boiling with dilute hydrochloric acid.

Andreasch[2] states that thiohydantoinacetic acid,



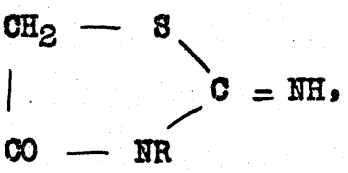
is obtained on heating at 105° a mixture of maleic or fumaric acid and water.

By heating a mixture of diphenylthiocarbamide and maleic acid for 1 to 2 hours at 140-144°, he obtains diphenylthiohydantoinacetic acid, melting at 188°.

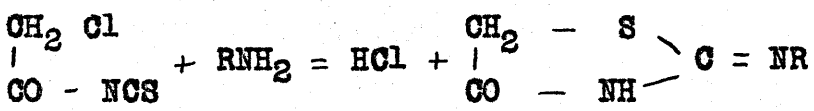
Augustus Edward Dixon[3], reviewing the evidence up to date concludes that while "---all the various methods hitherto employed for preparing monosubstituted

(1) Ann. 1894, 280, 233-246.
(2) Abs. Jr. Chem. Soc. (London) 70 (1896), 89; Monatsh, (1895), 16, 789-797.
(3) Dixon: Jr. Chem. Soc. (London) 71, 619 (1897).

thiohydantoins in which the rddicle is attached to nitrogen lead apparently to the production of a single form,



it seemed probable that their position-isomers might be obtained by acting with halogen-substituted acid thiocarbimides on the amines, according to the scheme,



The thiocarbimides were obtained by the halides of the corresponding halogen-substituted acids were treated with lead thiocyanate.

He obtained a small quantity of a substance melting at 175-176.5°, probably the phenylthiohydantoin (m.p. 178°), by treating aniline and chloracetylthiocarbimide in benzene.

With orthotoluidine he obtained orthotolylthiohydantoin hydrochloride (m.p. 212.5-213.5° uncorr.) and from this the base (m.p. 144-145°).

In boiling with baryta water this product gave thioglycollic acid (color test) showing that the S-atom is attached to the CH_2 of the glycolyl group.

By boiling the base in very dilute hydrochloric acid for some hours it was hydrolyzed to ammonia and a product (m.p. 119-120° corr.) which agreed "---in all repects with orthotolylthiocarbimido-

glycolide obtained[1] from alcohol, orthotolylthiocarbimide and monochloracetic acid." "A trace of orthotoluidine was detected."

He reasons that it is the ring-nitrogen which is displaced by hydrolysis, and writes the following provisional equations:

$$\begin{matrix}CH_2 - S \\ | \\ CO - NH\end{matrix}\!\!\diagup\!\!\diagdown C = NC_7H_7 + HCl + H_2O = \begin{matrix}CH_2 - S \\ | \\ CO - O\end{matrix}\!\!\diagup\!\!\diagdown C = NC_7H_7 + NH_4Cl$$

He now attempts to prepare the isomer, $\begin{matrix}CH_2 - S \\ | \\ CO - NTo\end{matrix}\!\!\diagup\!\!\diagdown C = NH$, by treating orthotolylthiourea and monochloracetate in alcoholic solution, but obtains the same product as before. He states that, "the apparent migration of the tolyl group might be accounted for by supposing the interaction to run the course,

$$\begin{matrix}CH_2\ Cl \\ | \\ COO\ Et\end{matrix} + \begin{matrix}HS \\ \\ NH_2\end{matrix}\!\!\diagup\!\!\diagdown C : NTo = HCl + EtOH + \begin{matrix}CH - S \\ | \\ CO - NH\end{matrix}\!\!\diagup\!\!\diagdown C : NTo,$$

but that the difficulty still remains as regards synthesis from thiourea and substituted chloracetamide, whereby the same products are obtained as from the substituted thiourea and ethylic chloracetate."

"In a paper by P. Meyer it is recorded[2] that phenylthiohydantoin, when boiled with dilute hydrochloric acid, yields the 'phenylthiocarbimidoglycolide' of Liebermann and Lange,[3] to which he

(1) Voltzkow: Ber., 13, 1580, (1880).
(2) Meyer: Ber., 14, 1662, (1881).
(3) Ber., 12, 597, (1879).

therefore assigns the formula $CH_2 - S \diagdown CO$ / $CO - NPh \diagup$,

Liebermann[1], after first adopting the above, decided[2] later in favour of the structure $CH_2 - S \diagdown C : NPh$ / $CO - O \diagup$, on the ground that chloracetic acid, acting on phenylthiourea, affords the same glycolide,[3]

$$Ph\,N : C(SH)(O\,Et) + CH_2 \cdot Cl - COOH = EtOH + HCl + PhN : C(S - CH_2)(O - CO)$$

According to Meyer[4], nevertheless, "this action might occur as follows:

$$CS(NHPh)(O \cdot Et) + CH_2\,Cl \cdot COOH = EtCl + CO(NHPh)(S - CH_2 \cdot COOH) = H_2O +$$

$CO(NPh - \diagdown CO)(S \cdot CH_2 \diagup)$, the ethylic chloride possibly escaping detection."

"A subsequent experiment, however, goes to confirm Liebermann's view, Evers having obtained the same compound[5] by warming chloracetic acid, in very weak alcohol, with phenyldithiourethane." The sulphuretted by-product was identified as ethyl mercaptan:

(1) Ber., 12, 1594, (1879).
(2) Ber., 13, 278, (1880).
(3) Liebermann: Ber., 13, 682, (1880).
(4) Loc. cit.
(5) Ber., 21, 975, (1888).

$$\begin{array}{l} CH_2\cdot Cl \\ | \\ COOH \end{array} + \begin{array}{l} HS \\ \\ EtS \end{array}\!\!\diagdown\!\!C : NPh = \begin{array}{l} CH_2 - S \\ | \\ CO - O \end{array}\!\!\diagdown\!\!C : NPh + EtSH + HCl.$$

"Taking, then, the constitution of phenylthiocarbimidoglycolide as correctly represented by the above formula, the corresponding thiohydantoin would be $\begin{array}{l} CH_2 - S \\ | \\ CO - NH \end{array}\!\!\diagdown\!\!C : NPh$, and the orthotolyl compounds, possessing, by analogy, like structures, would be $\begin{array}{l} CH_2 - S \\ | \\ CO - O \end{array}\!\!\diagdown\!\!C : NTo$ and $\begin{array}{l} CH_2 - S \\ | \\ CO - NH \end{array}\!\!\diagdown\!\!C : NTo$, forms identical with those arrived at through the synthesis from chlorinated acidic thiocarbimide."

Experiments designed to establish the structure of phenylthiohydantoin appeared to indicate that the reactions involved may be correctly represented by the following equations:

I. $$\begin{array}{l} CH_2 - S \\ | \\ CO - NPh \end{array}\!\!\diagdown\!\!C : NH + H_2O = NH_3 + \begin{array}{l} CH_2 - S \\ | \\ CO - NPh \end{array}\!\!\diagdown\!\!CO, \text{ (+trace of aniline)}$$

II. $$\begin{array}{l} CH_2 - S \\ | \\ CO - NH \end{array}\!\!\diagdown\!\!C : NPh + CS_2 = PhNCS + \begin{array}{l} CH - S \\ | \\ CO - NH \end{array}\!\!\diagdown\!\!CS,$$

III. $$\begin{array}{l} CH_2 - S \\ | \\ CO - NH \end{array}\!\!\diagdown\!\!C : NH + NH_2\,Ph = \begin{array}{l} CH_2 - S \\ | \\ CO - NH \end{array}\!\!\diagdown\!\!C : NPh + NH_3.$$

His conclusions were that the results showed:

A. that one thiohydantoin alone is the product of interaction between:

(a) monosubstituted thiourea and ethylic chloracetate.

(b) thiourea and substituted chloracetamide.

(c) chlorinated acidic thiocarbimide and organic base.

B. That the constitution of phenylthiohydantoin and its allies (judging from the interaction with carbon bisulphide) should be represented by the general formula:

$$\begin{matrix} CH_2 - S \\ | \quad\quad \diagdown \\ CO - NH \quad\quad C : NR. \end{matrix}$$

He found that, as in the case with aniline, para-toluidine and the same thiocarbimide, failed to give the hydantoin, yielding only chloractoparatoluidide $CH_2\,Cl \cdot CO \cdot NH \cdot C_7H_7$.

With methylaniline he obtained methylphenylthiohydantoin, (m.p. 129–130° corr.)

$$\begin{matrix} CH_2\,Cl \\ | \\ CO - NCS \end{matrix} + NHMePh = \begin{matrix} CH_2 - S \\ | \quad\quad \diagdown \\ CO - N \end{matrix} C \cdot NMe\,Ph + HCl .$$

With alkali it undergoes decomposition as follows:

$$\begin{matrix} CH_2 - S \\ | \quad\quad \diagdown \\ CO - N \end{matrix} C - N{=}MePh + 3H_2O = \begin{matrix} CH_2 - SH \\ | \quad\quad \diagdown \\ CO - OH \end{matrix} + CO_2 + NH_3 + NHMePh.$$

Boiled with dilute HCl for 30 minutes, methyl-[illegible], aniline, and a trace of ammonia are obtained.

"These reactions leave no room for doubt regarding the structure of the compound under consideration——"

"This compound is the first representative hitherto described of a class of thiohydantoins having two substituting radicles attached to a single nitrogen atom. Isomeric forms are known, derived from symmetrical disubstituted thiocarbimides, for example, a

diphenylthiohydantoin, produced by acting with chloracetic acid on thiocarbanilide[1] and it seemed probable that members of the former class would be obtained by the interaction of this acid with the corresponding "Unsymmetrical disubstituted thioureas, thus:

$$\begin{matrix} CH_2 - Cl \\ | \\ CO - OH \end{matrix} + \begin{matrix} HS \\ \diagdown \\ NH \end{matrix} \!\!=\!\! C - NXY = HCl + H_2O + \begin{matrix} CH_2 - S \\ | \\ CO - N \end{matrix} \!\!\diagup\!\!= C - NXY.$$

"

Acting upon this idea, he prepared the same methylphenylthiohydantoin from α Methylphenylthiourea and ethylmonochloracetate in alcoholic solution. (m.p. 129-130°).

$$\begin{matrix} CH_2 - Cl \\ | \\ CO - OEt \end{matrix} + \begin{matrix} HS \\ \diagdown \\ NH \end{matrix} \!\!=\!\! C - NMePh = H_2O + \begin{matrix} CH_2 - S \\ | \\ CO - N \end{matrix} \!\!\diagup\!\!= C - NMePh \cdot HCl,$$

m.p. 193-194°.

With benzylaniline, the corresponding thiohydantoin was obtained, melting at 118-119°. The hydrochloride was not formed as in the previous case.

Boiled for an hour in dilute hydrochloric acid, it yielded benzylanilinehydrochloride melting at 202-203°. The free base was secured melting at 35-36°. Another substance melting at 123-124° which was doubtless the dioxythiazole of Claesson[2] and Heintz[3].

$$\begin{matrix} CH_2 - S \\ | \\ CO - N \end{matrix} \!\!\diagup\!\!= C - NB_zPh + H_2O = \begin{matrix} CH_2 - S \\ | \\ CO - NH \end{matrix} \!\!\diagdown\!\! CO + B_z\,NHPh.$$

(1) Lange: Ber., 12, 595, (1879).
(2) Claesson: Ber., 10, 1353, (1877).
(3) Heintz, Ann., 136, 232 (1865).

Allylphenylthiocarbamide and Chloracetamide were "caused to interact in the hope of obtaining two isomeric disubstituted thiohydantoins."

(a) $CH_2 - Cl$ / $CO - NH_2$ + HS / $PhNH$ \ $C : NAll = NH_4Cl +$ $CH_2 - S$ / $CO - NPh$ \ $C : NAll.$

(b) $CH_2 - Cl$ / $CO - NH_2$ + HS / $AllNH$ \ $C : NPh = NH_4Cl +$ $CH_2 - S$ / $CO - NAll$ \ $S : NPh.$

The "materials were dissolved in alcohol and the mixture concentrated on the water bath." The resultant product, separated from impurities, "on cooling became very tenacious but did not crystallise." "In the course of a week a slight deposition of crystals began, which was not materially increased after another week's standing; the amount was two small to admit of purification." "No chemical difference was observed between their behavior and that of the oil."
A solution of the oil in alcohol "was darkened by ammoniacal nitrate of silver, and slightly desulphurised on boiling with alkaline lead tartrate (probably owing to the presence of a trace of unchanged allylphenylthiocarbamide)." Boiled for several hours with somewhat dilute hydrochloric acid, the solution "reacted strongly for aniline, and when heated with excess of potash, freely evolved an alkaline gas having a pungent ammoniacal odour, but giving with Nessler's solution a pale primrose-yellow precipitate, and hence consisting, not of ammonia, but of Allylamine."

"FRom the above results, it would appear that the oil contains both the expected isomeric forms, although, in this instance, they could not be isolated; the action may be formulated thus:

1. $\begin{matrix} CH_2 - S \\ | \\ CO - NAll \end{matrix}\!\!\diagdown\!\!C : NPh + H_2O = \begin{matrix} CH_2 - S \\ | \\ CO - O \end{matrix}\!\!\diagdown\!\!C : NPh + AllNH_2$.

2. $\begin{matrix} CH_2 - S \\ | \\ CO - NPh \end{matrix}\!\!\diagdown\!\!C : NAll + H_2O = \begin{matrix} CH_2 - S \\ | \\ CO - O \end{matrix}\!\!\diagdown\!\!C : NAll + PhNH_2$. "

Aniline and α-bromopropionylthiocarbimide, (CH_3 - CHBr - CO - NCS), react but the product was not secured in a pure state.

With orthotoluidine this imide gave the hydantoin melting at 72-73°/ $CH_3 - \begin{matrix} CH - S \\ | \\ CO - NH \end{matrix}\!\!\diagdown\!\!C : NC_7H_7$.

It is decomposed by alkali and the iron test gives a purplish coloration, "due to the presence of methylthioglycollic acid." This product however was apparently not isolated. Hydrolysis in acid solution is not reported. Dixon here appears to take considerable for granted.

$$CH_3 \cdot \begin{matrix} CH - S \\ | \\ CO - NH \end{matrix}\!\!\diagdown\!\!C : NTo + 3H_2O = \begin{matrix} CH_3 \cdot CH - SH \\ | \\ CO - OH \end{matrix} + CO_2 + NH_2To + NH_3.$$

With methylaniline he obtains the corresponding hydantoin melting at 129-130°.

$$CH_3 \cdot \begin{matrix} CH - S \\ | \\ CO - N \end{matrix}\!\!\diagdown\!\!C : N(CH_3) \cdot C_6H_5.$$

Boiled with dilute alkali for a few minutes "it gives the iron reaction for methylthioglycollic acid."

Hydrolysis with acid is not recorded.

With benzylaniline, in absolute alcohol, a clear, yellow, very tenacious oil was obtained. Boiled with dilute alkali it gives the test for "methylthioglycollic acid." The product, however, apparently was not obtained pure inasmuch as the analysis for sulphur showed 9 percent as against 10.82 calculated for the thiohydantoin.

Aniline with α-bromobutyrylthiocarbimide ($CH_3 \cdot CH_2 \cdot CHBr \cdot CO \cdot NCS$) reacts to form a product melting at 148-149°, when analysis corresponds to that for the thiohydantoin $C_2H_5 \cdot CH - S \backslash C : NC_6H_5$ (with $CO - NH /$).

It may be "precipitated, unchanged, from caustic alkali solutions." "This is the only case in which an attempt to prepare a thiohydantoin from aniline and a halogen-substituted thiocarbimide was successful." Hydrolysis is not recorded.

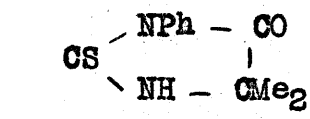
$$C_2H_5 \cdot CHBr \cdot CONCS + C_6H_5NH_2 = C_2H_5 \cdot CH - S \backslash C : NC_6H_5 + HBr.$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CO - NH /$$

A thiohydantoin is also obtained with orthotoluidine melting at 95-96.5°.

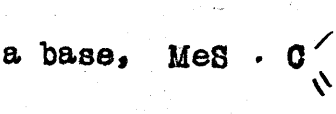
Boiled with alkali, the ferric chloride test gives "a transient, purplish coloration due probably to the presence of ethylthioglycollic acid." Hydrolysis in acid solution is not recorded.

"Derivatives are known of substances isomeric with the thiohydantoins, but having the glycolyl

group attached entirely through the nitrogen; thus, by acting with methylic iodide and potash on β-phenyl-α-dimethylthiohydantoin,



, a base,



, is obtained(1). This compound is related to the parent substance in the same way as, for example, methyl-ψ-thiourea to thiocarbamide, and such a form might therefore be classified as a ψ-thiourantoin."

Rizzo(2) states that chloracetanilide and ammonium thiocyanate give thiocyanacetanilide melting at 176°, but Frerichs and Beckurts(3) found this to be the phenylthiohydantoin of P. Meyer. Grothe(4) had just described a number of compounds as normal thiocyanacetanilides. Beckurts and Frerichs repeated the work and concluded that by the action of potassium thiocyanate on chloracetanilide, there first results the rhodanacetanilide described by Grothe as melting at 86-87°. On heating an alcoholic solution of this compound they found that Meyer's phenylthiohydantoin was produced.

These authors then undertake the examination of Grothe's compounds in order to determine whether they are normal- or isothiocyanates. They believed their results to show that, with the exception

(1) Marckwald, Neumark, and Stilzner: Ber., 24, 3295, (1891).
(2) Centrbl., 1898, II., 296.
(3) Arch. Pharm., 238, 615 (1900).
(4) Arch. Pharm., 238, 610 (1900).

of rhodanacetmethylanilide, the substances are normal thiocyanates.

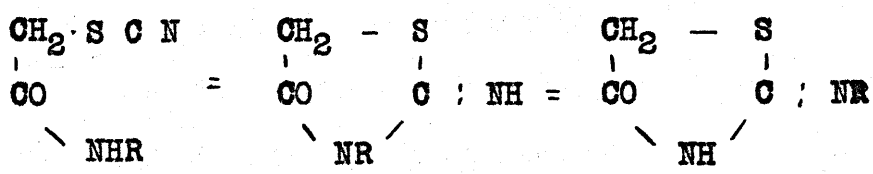
Wheeler and Johnson[1] have shown that "unsymmetrical acetylthioureas are transformed into symmetrical isomers on heating."

$H_2N - CS - N(C_6H_5) \cdot CO \cdot CH_3 = CH_3CONH \cdot CS \cdot NHC_6H_5$,

or

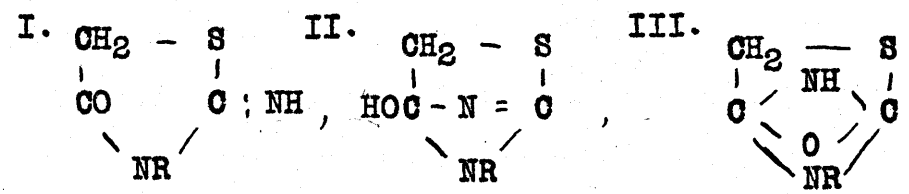
$HN = C(SH) \cdot N(C_6H_5) \cdot CO \cdot CH_3 = CH_3CO \cdot NH \cdot C(SH) = NC_6H_5$,

and these same workers have also shown[2] "that a thiocyanacetanilide is capable of metastatic change into a labile pseudothiohydantoin and then into a stabile isomer".



They summarize the work of previous workers on the structure of the isothiohydantoin.

Treat B. Johnson[3] following up this work states in part: "Three possible formulas which might be assigned to the labile pseudothiohydantoins were considered by us but no conclusive experimental evidence was produced that established any one of these structures:



(1) Wheeler and Johnson: Am. Chem. Jr. 27, 270 (1902).
(2) " " " " " " 28, 121 (1902).
(3) Johnson T. B. : Jr. Am. Chem. Soc. 25, 484, (1903).

"The structure of the stabile pseudothiohydantoin was definitely established by the fact that unsymmetrical benzyl-phenylthiourea and ethylchloracetate gave the same compound as was obtained by treating the stable phenylpseudothiohydantoin with alkali and benzyl chloride, showing that the phenyl group is attached to the nitrogen outside the ring. This is the formula assigned by Dixon(1)." The other chloracetanilides studied "have been

chloracet-B-napthalide,

chloracet-m-Xylidide,

chloracet-m-nitroanilide,

and chloracet-p-bromanilide."

The "structure to be assigned to the intermediate products formed in these rearrangements is still left undecided."

The following outline of the work of one series is given as typical:

Chloracet-m-nitroanilide, $ClCH_2CONH \cdot C_6H_4 \cdot NO_2$.

"This anilide was prepared from chloracetylchloride and m-nitroaniline. It crystallized from alcohol in plates and melted at 101-102° C."

Labile m-Nitrophenylpseudothiohydantoin. This body was obtained by boiling in benzene, chloracet-m-nitroanilide with potassium thiocyanate for twenty minutes. It crystallized from alcohol in the form of plates and melted at 183-184° C.

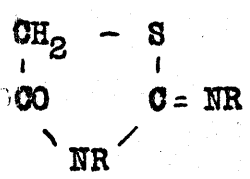
Action of Alkali. This hydantoin, melting at

(1) Dixon: Jr. Chem. Soc. (London) 71, 620.

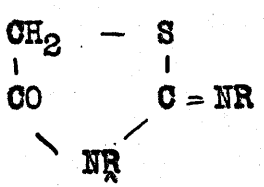
183-184°, dissolved in cold sodium hydroxide solution. On neutralizing with acetic acid a mass of needles separated. They were purified by crystallizing from benzene and melted at 133-134° C. A nitrogen determination agreed with that calculated for m-nitrophenylcyanamide."

Wheeler and Jamieson[1] have found that certain stable pseudothiohydantoins give diacetyl derivatives with acetic anhydride and that these acetyl compounds do not behave like acetoacetic acid derivatives. "This would seem to indicate that the group, $-CO-CH_2 \cdot S-$, is not present in the stable pseudothiohydantoins."

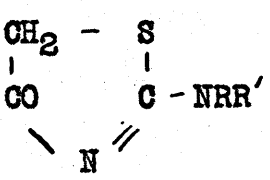
The non-substituted pseudothiohydantoins condense with benzaldehyde and behave like other compounds[2]. "We have now found that substituted pseudothiohydantoins represented by formulas I, II, and III, also condense with aldehydes and oxalic ester. They therefore behave in a tautomeric manner with acetic anhydride and aldehydes."



I.



II.



III.

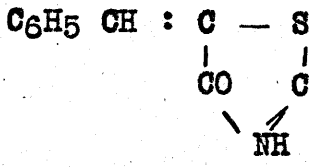
Their condensation products resemble the corresponding

(1) Wheeler and Jamieson: Jr. Am. Chem. Soc. 25, 366 (1903)
(2) Andreasch: Monatsh. Chem., 8, 407.

products of rhodanic acid, (∝-μ-diketotetrahydrothiazole), and the non-substituted pseudothiohydantoins with salicylic and cinnamic aldehydes described by Andreasch and Zipser[1].

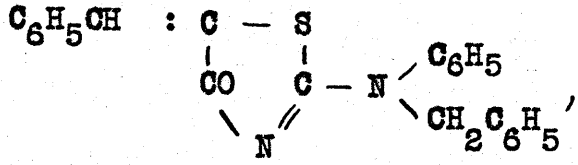
Among the compounds described are,

∝-keto-μ-phenylimido-β-benzaltetrahydrothiazole



m.p. 251-252°.

Benzalphenylbenzylpseudothiohydantoin,



m.p. 186-187°

and others of a similar type.

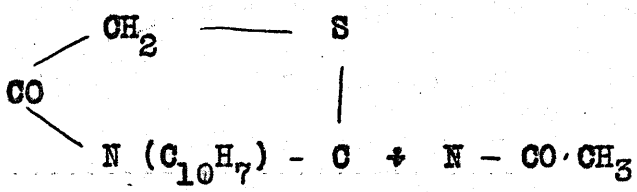
T. B. Johnson, Walbridge, McFarland and Cramer[2] in a second paper on molecular rearrangements of thiocyanacetanilides into labile and stable pseudothiohydantoins describe a number of labile compounds and their stable isomers. In this paper a record of the following compounds is found:

Chloracetyl-β-napthalide, m.p. 117-8°, prepared from chloracetyl chloride and β-napthylamine.

Labile, β-npathyl-ψ-thiohydantoin, m.p. 147°.

2,- Acetylimino - 3-β-napthyltetrahydrothiazole, m.p. 139-140°,

(1) Chem. Ztg., 26, 54, 623 (1902).
(2) J. Am. Chem. Soc. 25, 483-491 (1903).



N ($C_{10}H_7$) - C + N - CO·CH_3

β-napthylacetothiohydantoic acid, obtained as a by-product, m.p. 167-173° .

Boiled with dilute alcohol the labile thiohydantoin it rearranges to the stable isomeride, (m.p. 213-14° with decomposition).

When ammonium chloracetate is boiled with β-napthylthiocarbamide in alcoholic solution, β-napthyl-ψ-thiohydantoic acid is formed, (m.p. 195-230°). Warming with glacial acetic acid converts this into the stable β-napthyl-ψ-thiohydantoin, the acetyl derivative of which melts at 142-143° . The stable form with benzaldehyde gives 4 - keto - 5 - benzylidene -2- β-napthyl-iminotetrahydrothiazole, m.p. 272° . In addition, the metaxylyl labile and stable hydantoins and the acetyl derivatives of the latter are described, as is also the labile form of metanitrophenyl-ψ-thiohydantoin, m.p. 183-184° .

Dixon and Joachim[1] in a paper on "Acyl Substituted Isothiohydantoins," are quoted as follows:

"Concerning the acyl substituted isothiohydantoins, practically the whole of our knowlege, embodied in two papers, one by Wheeler and Johnson (Amer. CHem. J, 1902, 28, 121) and the other by Johnson, Wallbridge,

(1) Jr. Chem. Soc. (London) Trans. 1.

McFarland, and Cramer (J. Amer. Chem. Soc., 1903, 25, 483), may be summarized as follows: isoThiohydantoin containing an aryl group, R, in the ring, by treatment with thiolacetic acid or with acetic anhydride, yield acetyl derivatives of the form, $N_6CO \cdot N : C \begin{matrix} NR - CO \\ S - CH_2 \end{matrix}$, the phenylic member of this class being producible also from either phenylisothiohydantoic acid or thiocyanoacetanilide by means of acetic anhydride. Further, ordinary β-napthylisothiohydantoin gives with acetic anhydride a derivative,

$$C_{10}H_7 - N : C \begin{matrix} N(COMe) - CO \\ S \quad\quad\quad CH_2 \end{matrix},$$

the corresponding o - or p-tolylisothiohydantoin, under like treatment, affording a diacetyl derivative.

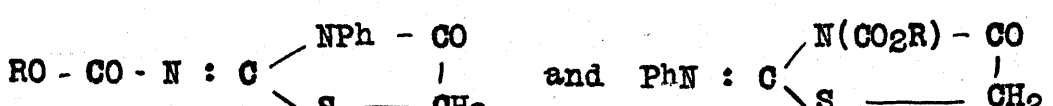
No purely acidic substitution derivative of isothiohydantoin seems yet to have been described. It was found, too, by Dixon and Taylor (T., 1912, 101, 558) that ab-acetylphenylthiocarbamide, when heated with chloroacetyl chloride, yields ordinary phenylisothiohydantoin, the acyl substitutent of the thiocarbamide being expelled in the form of acetyl chloride. Similar results were observed with tri-substituted thiocarbamides containing the acetyl, the benzoyl, or the carbethoxy-radicle, together in each case with two hydrocarbon residues.

Such tri-substitution derivatives are not

particularly stable. More recent investigation has shown that less highly substituted thiocarbamides containing the group ·CO·OR (where R = alkyl or aryl), by means of chloroacetyl chloride are transformable into isothiohydantoins without the loss of that group. Thus, for example, carb-ethoxyisothiohydantoin may be obtained from carbethoxythiocarbamide, or a phenylcarbethoxy-analogue from ab-phenyl-carbethoxy-thiocarbamide.

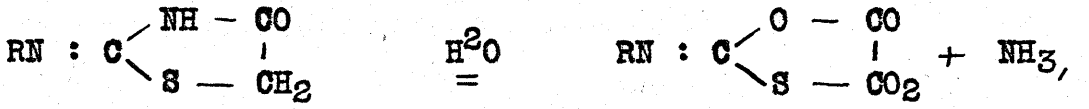
Consistently with the observations of Dixon and Taylor (loc. cit.) it has been found that ethyl chloroacetate, in alcoholic solution, fails to attack the mono-substituted carboalkyloxythiocarbamides; if, however, calcium carbonate is added to the mixture, interaction takes place, with the formation of the corresponding mono-substituted isothiohydantoins. With di-substituted thiocarbamides, RO·CO·NH·CS·NHPh, or with mono-substituted carboaryloxythiocarbamides, however, ethyl chloroacetate does not react, either directly or in the presence of calcium carbonate.

So far as their method of production is concerned, the carboalkyloxyisothiohydantoins referred to above might have either (or both) of the configurations represented by the formulae:



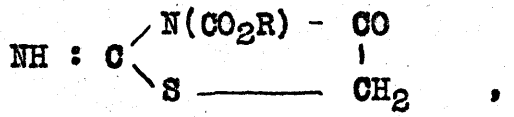
(I.) (II.)

When hydrolized by means of hot dilute hydrochloric acid, they yield carbon dioxide, ammonium chloride, and 'phenyldioxythiazole.' Now, Dixon has shown (J., 1897, 71, 623) that in the transformation by which a substituted isothiohydantoin furnishes a substituted 'dioxythiazole' , the nitrogen member of the parent ring is exchanged for an oxygen atom, thus:

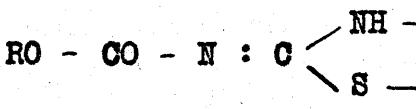


whence it follows that the foregoing carboalkyloxyisothiohydantoins have the constitution represented by formula II.

Judgement in the case of mono-substitution derivatives is a less simple matter. Analogy would suggest the formula



which also is consistent with the fact that on hydrolysis by acid, they rapidly yield carbon dioxide, ammonia, and dioxythiazole. Moreover, that the latter does not result through the hydrolysis of isothiohydantoin, possible formed from a compound,



is clear; because, whilst the actual hydrolysis is speedily accomplished, that of isothiohydantoin, in like circumstances, is very slow, yet the presence of this compound could not be detected in the mixture.

Nevertheless, it is conceivable that a substituted dioxythiazole, $CO_2R - N : C\begin{matrix} O - CO \\ \diagdown\!\diagup \\ S - CH_2 \end{matrix}$, might be formed and then hydrolysed, with elimination of the group $-CO_2R$. Substances of the class last formulated are unknown.

Through the action of chloroacetyl chloride on A-acetyl-b-carbethoxythiocarbamide it should be possible to synthesise a compound having the structure $CO_2\,Et - N : C\begin{matrix} NH - CO \\ \diagdown\!\diagup \\ S - CH_2 \end{matrix}$, and if this should prove isomeric with that from carbethoxy-thiocarbamide itself, decision would be easy. In practice, however, such a check could not be applied, all attempts to produce a thiocarbamide of the required configuration being unsuccessful.*

Frerichs and Förster[1] describe β. phenyl-amidothiohydantoin, to which they assign the structure

$$HN : C\begin{matrix} N(NHPh) \\ \diagdown\!\diagup \\ S - CH_2 \end{matrix}CO \quad , \quad (\text{m.p. } 176^{\circ}),$$

prepared from ethylthiocyanoacetate and phenyl hydrazine. A KOH solution is colored violet red. This compound is also formed from monochloracetic acid and phenylthiosemicarbazide.

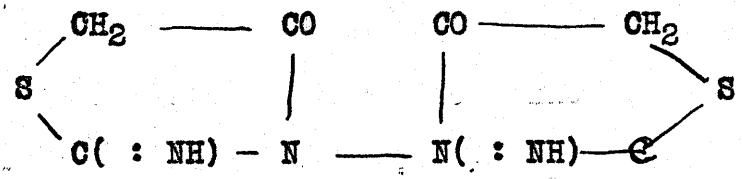
Thiocyanoacetic acid and hydrazine hydrate give hydrazine isothiocyanoacetate.

$S : C : NCH_2 \cdot CO_2 \cdot NH_3 \cdot NH_2$, m.p. 87-90° .

When the ethyl ester is used and a water solution

(1) Ann., 371, 227-57 , (1909).

heated, β, β-bisthiohydantoin results.

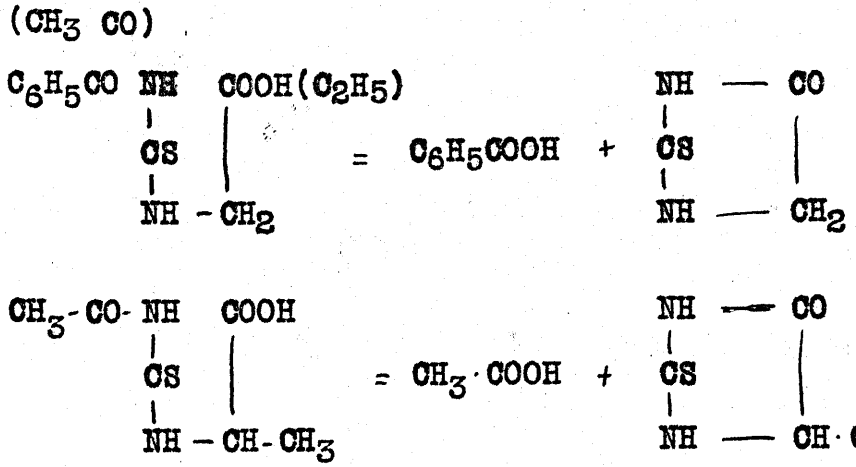


Wheeler, Nicolet and Johnson[1] in a paper on "Hydantoins" prepare and describe some N-acyl-derivatives of hydantoic and thiohydantoic acids,

R - CO - NH-CO-NH-CH_2-COOH.

R - CO - NH-CS-NH-CH_2-COOH.

Their behavior on hydrolysis and the reactivity of their methylene hydrogens towards aldehydes are investigated. When digested with hydrochloric acid they are transformed into cyclic compounds. Benzoyl- and acetyl-thiohydantoic acids undergo hydrolysis and 2-thiohydantoin is formed.



"These nitrogen-unsubstituted thiohydantoins represent new types of thiohydantoins." The plain ethylthiohydantoate, NH_2 - CS - NH-CH_2-COO-Et, does not undergo condensation under similar conditions." A number of

(1) Am. Chem. Jr. 46, (1911), 456.

derivatives of this type were prepared and described. A continuation of this investigation by Wheeler and Grust[1] is reported in a paper on "The Action of Potassium Thiocyanate on Pyrrolidonecarbocyclic Acid, 2-Thio-hydantoin-4-Propionic Acid."

M. Emmanuel Escot[2], in a paper entitled (Study and Synthetical Preparation of Aryl Thio-hydantoins", states:

"Disubstituted ψ-thiohydantoins, readily prepared by the action of monochloro- or monobromo-acetic acid on the s-arylthiocarbamides (compare Abstra., 1904, i, 869), are crystalline compounds, decomposed by alkalis yielding the corresponding S-arylcarbamides according to the equations:

$$RN : C\begin{matrix}\diagup SH \\ \diagdown NHR\end{matrix} + CH_2\,CL \cdot CO_2\,H = RN : C\begin{matrix}\diagup S - CH_2 \\ \diagdown NR - CO\end{matrix},$$

$$RN : C\begin{matrix}\diagup S - CH_2 \\ \diagdown NR - CO\end{matrix} + 2\,H_2O = CO(NHR)_2 + HS - CH_2 \cdot CO_2 \cdot H.$$

Di-o-tolyl-ψ-thiohydantoin forms slightly yellow, octahedral crystals melting 4° lower than the corresponding thiocarbamide, is slightly soluble in water and readily so in boiling alcohol or cold xylene, toluene, or chloroform. Di-p-tolyl-ψ-thiohydantoin crystallizes from alcohol in white prisms and melts at 183°; the β-isomeride possesses similar properties. Diphenyl-ψ-thiohydantoin

(1) Am. Chem. Jr. 47, 242 (1912).
(2) Compt. redd., 1904, 139, (1031-1032).

crystallizes from alcohol and melts at 174°. "

Dixon and Taylor[1] state:

"When the chloride of a carboxylic acid is brought into contact with a hydrocarbon-monosubstituted thiourea, direct union occurs, the hydrochloride being formed of a basic substance, $R \cdot NH \cdot C(=NH)(-S \cdot CO \cdot R)$ in which the acid radicle, $R \cdot CO$ is engaged with the sulphur of the thiourea[2]. (For the sake of simplicity, no reference is here made to the tantomeric variants, which may, and probably do, exist; for example,

$RN : C(NH_2)(-S-COR)$, etc.)

On the other hand, when chloracetic acid reacts with such a thiourea, the chlorine atom, as before, withdraws the hydrogen of the SH-group, the sulphur of which, engaging with the residue of the acetic acid, forms a so-called "thiohydantoic" acid,

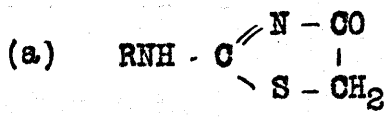
$RNH \cdot C(NH) \cdot S \cdot CH_2 \cdot COOH$:

By loss of the elements of water, this undergoes, more or less completely, condensation into the isothiohydantoin, $RNH \cdot C(=N-CO-)(-S-CH_2-)$.

If, however, to a monosubstituted thiourea, chloroacetyl chloride is presented, both the hydrogen

(1) Proc. Chem. Soc., 28, 54 ; (1913) J. Chem. Soc., 101, 558-70).
(2) Dixon and Hawthorne: Trans., 1907, 91, 122).

atoms are eliminated as hydrogen chloride; in which case the product may obviously possess either of the following constitutions:



(a) RNH · C(=N – CO; S – CH_2) (b) RNH · C(=N – CH_2; S – CO) .

Experiment has shown[1] that from these and similar materials, at temperatures down to -8°, form (a) alone is produced; and hence, of the two groups, -COCl and -CH_2Cl, the latter seems preferentially to engage with the SH of a thiourea.

Further, it has been shown[2] that acid chlorides, R - COCl, fail to combine with thioureas containing already an acyl group. If, therefore, chloracetyl chloride were presented to an acyl trisubstituted thiourea of the form, R_2 N - C(NAc) - SH, it might be anticipated that a somewhat complex acid chloride would result, as shown by the following equation: $R_2N \cdot C(NAc) - SH + ClCH_2 - COCl = HCl + R_2N \cdot C(NAc) \cdot S \cdot CH_2 \cdot COCl$.

Experiment has curiously failed to justify this anticipation."

"Experimental."

(The following compounds were prepared and described.)

v-Diphenyl-n-benzoylthiourea and Chloracetyl

(1) Dixon and Taylor: Trans. 1908, 93, 21).
(2) Dixon and Hawthorne, loc. cit., 141).

Chloride.

$Ph_2 N - C(N - COPh) - SH + ClCH_2 \cdot COCl =$

$Ph_2 N \cdot C(N \cdot COPh) \cdot S \cdot CH_2 \cdot COCl + HCl.$

melting point = 198° (corr.).

"As the parent material[1] is by no means readily desulphurized by lead salts, the failure of the product to yield its sulphur to alkaline solution of lead was not conclusive evidence that the sulphur had become singly linked in the new molecule. Nevertheless, that this was the case was established by digesting the substance with alcoholic potassium hydroxide; for the residue, when acidified and treated with dilute ferric chloride followed by ammonia, gave Andreasch's reaction for thiolacetic acid, $SH \cdot C H_2 - CO_2H$ [2], hence showing the presence of the group $- S - CH_2 - CO$.

The conjecture that the above compound was the hitherto unknown diphenylisothiohydantoin, $Ph_2N - C(=N - CO - S - CH_2)$, was verified by the result of a sulphur determination.

All these results may be summed up by the equation: $Ph_2 N \cdot C(N \cdot COMe) - SH + ClCH_2 - COCl =$

$$Ph_2 N - C(=N - CO - S - CH_2) + HCl + Me - COCl.$$ "

etc.

(1) Dixon and Taylow: Trans., 1908, 93, 693.)
(2) Ber., 1879, 12, 1385.)

"The general outcome of the present inquiry, and of certain other similar investigations may now be summarized approximately as follows:

(1) The chlorides, R - COCl, of mono-carboxylic acids unite directly with thiourea, or with its mono-, di-, or tri-substitution derivatives, to yield substances of the form XYN - C(NZ) - S - COR, HCl, X, Y, and Z being hydrogen or hydrocarbon radicles. Whether these are hypochlorides, containing a quinquevalent nitrogen atom, or sulphonium chlorides is still uncertain.

If the thiourea contains an acyl substituent, such union does not occur.

In the case of thiourea and its monosubstitution derivatives, withdrawal of the combined halogen acid may be followed by a migration of the acyl radicle to one of the nitrogen atoms of the thiourea. If the thiourea is monosubstituted, the acyl radicle leaving the sulphur tends to migrate first to the nitrogen atom which already holds a hydrocarbon radicle; from this position it may usually be caused to move (and sometimes moves spontaneously) to the other non-substituted nitrogen atom.

(2) Chloracetyl chloride acts on thiourea and its hydrocarbon mono- or di-substitution derivatives solely by ring-closing, with production of isothiohydantoins (from the work of various observers, it appears that this is true also of chloracetic acid.)

Thioureas containing an acyl radicle are attacked by chloracetyl chloride, with expulsion of that radicle (as an acyl chloride), and formation of the corresponding non-acylated isothiohydantoin; but aa-acetylphenylthiocarbamide yields the same compounds as that obtained from the ab-derivative.

Trisubstituted thioureas, including purely hydrocarbon radicles, unite directly with chloroacetyl chloride to form hydrochlorides, X Y N · C(NZ) – S – CO – CH_2Cl, HCl (or, possibly sulphonium chlorides).

(3) Ethyl chloroacetate behaves towards thiourea and towards its hydrocarbon mono- or di-substitution derivatives in the same way as does chloroacetyl chloride. If, however, the thiourea contains an acyl substituent, no interaction takes place."

V. Bror Holmberg[1] records that the sodium salt of N-phenyl-α-keto-β-ethoxymercapto-oxazalidine, Ph N – CO – CH_2 – O – C (O Et)·SH, reacts with Cl·CH_2·CO·N H·Ph to give Ph N – C(: NPh) – S – CH_2 CO, or Ph N – CO – S – CH_2 – C : N Ph.

T. B. Johnson and Joseph A. Ambler[2] find that pseudothiohydantoinacetic acid,

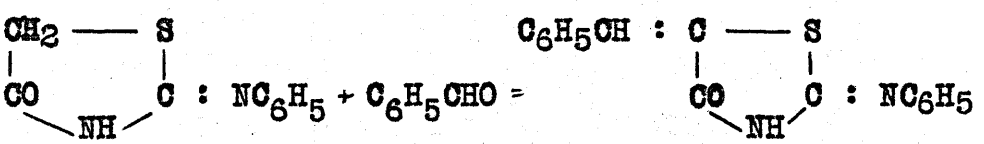
$$HO_2\,CCH_2\cdot CH \begin{cases} CO - NH \\ S - C : NH \end{cases}$$

is

(1) C. A. (1912).
(1) J. prakt. Chem., 84, 634-86 (Abstracted 1912). This reference must however be a mistake, for the volume referred to does not contain such an article.
(2) C. A. (1913), 1164: (Am. Chem. J. 48, 197-205)(1912).

obtained by heating thiourea with fumaric acid with water in a closed tube at 105°. Optical isomers were not secured.

They state in this paper, "that certain pseudothiohydantoins, which contain the thioglycollic grouping, $-S-CH_2-CO-$, behave in a tantomeric manner with respect to their reactions with aldehydes and acetic anhydride. For example, the methylene hydrogens in the stable arylhydantoins (I), and also those of the disubstituted pseudothiohydantoins (III) and (IV), are capable of reacting with aldehydes in a manner similar to that of benzyl cyanide, forming condensation products corresponding to the hydantoin[1] (II).



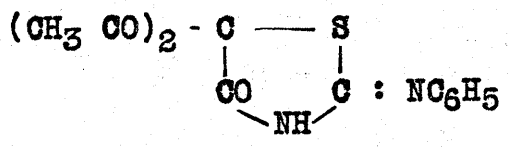
I. II.

III. IV.

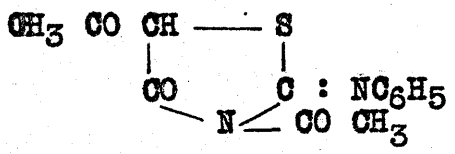
On the other hand the stable hydantoins (I) react smoothly with acetic anhydride, forming stable diacetyl derivatives."[2] "No definite constitution, however, was assigned to these diacetyl compounds,

(1) Wheeler and Jamieson: J. Am. Chem. Soc. 25, 366 (1903).
(2) Wheeler and Johnson: Am. Chem. Jr. 28, 121.

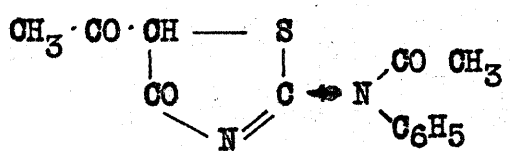
but it was shown that they do not behave as acetoacetic acid derivatives. In other words the hydrogens of the methylene group (CH_2) are not directly replaced by both acetyl groups as represented in (V) or by one acetyl radical as represented in the two hydantoins (VI) and (VII). This was established by the fact that these diacetyl derivatives are insoluble in alkali. Formula (VIII) is not to be considered since it represents an unstable structure - an imido acid anhydride[1], which would be expected to rearrange into its stable isomer"(VI).



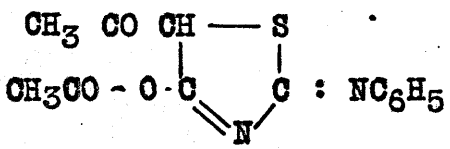
V.



VI.



VII.



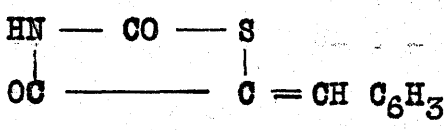
VIII.

They find that the brucine salt of pseudothiohydantoinacetic acid is capable of undergoing a change in an aqueous solution, and that this can be followed quantitatively by means of the polarimeter."

"The variations in specific rotation are not due to the phenomenon of hydrolytic dissociation, but are probably in response to a desmotropic change in the pseudothiohydantoin nucleus of the salt."

(1) Wheeler and Johnson: Am. Chem. Jr. 30, 24.

Frank Kucera[1] records the preparation of β-Methylene dioxybenzalmustard oil acetic acid,

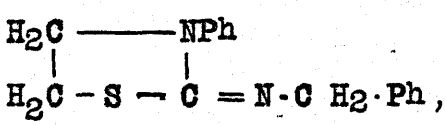


from piperonal and mustard oil acetic acid with the use of Ac·O·Na .

β-Benzalisothiohydantoin was obtained from isothiohydantoin and BzH with NaOH.

Ethyl thiohydantoin with K Cl O_3 and HCl gave HO_2 C·CH_2 SO_3 H and Et NH CO NH_2.

N-Benzyl-γ-phenyldihydrothiohydantoin,



was obtained from Ph·NHC(SH) : N·CH_2·Ph and C_2 H_4 Br_2, and n-Phenyl-γ-p-tolyldihydrothiohydantoin from $C_2H_4Br_2$ and Ph·N : C(≤H)·N*H*C_7H_7 .

H. Beckurts and G. Frerichs[2] are here quoted as follows from an article entitled "Concerning Arylamides of Thiocyanaceticacids and Arylthiohydantoins."

"F. Hurdelbrink has investigated further, by way of a great number of substituted chloracetarylamides, the action, which was first studied carefully by us, of thiocyanogen salts on chloracetarylamides. The results of these investigations correspond with those obtained by us. The chloracetarylamides are easily obtained, when the arylamide is dissolved in

(1) C. A. (1914), 1573: (Monatch., 35, 137-57).
(2) Archiv. D. Pharm. 253, 233-65 (1915).

benzene and chloracetyl chloride, diluted with benzene, is added to the solution. When potassium thiocyanate is permitted to react with the chloracetyl compounds, in some cases, an isothiocyanacet compound,

$$S = C = N - CH_2 - CONHR ,$$

is obtained, which however very quickly rearranges to the normal thiocyanacet compound,

$$N \equiv C - S - CH_2 - CONHR.$$

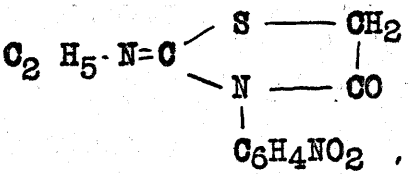
In the majority of cases the latter compound is immediately obtained and the isthiocyanacetyl compound can scarcely be isolated in the pure state.

When one heats the normal thiocyanacetyl compounds for quite a period with water, or even dissolved in glacial acetic acid, a molecular rearrangement takes place:

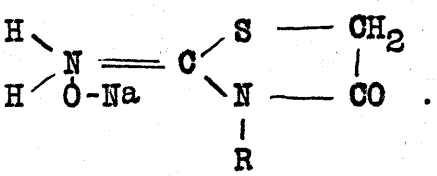
$$N \equiv C - S - CH_2 - COR = HN \begin{array}{l} C \begin{array}{l} S - CH_2 \\ N - CO \end{array} \\ \quad\quad\quad\

and the solution heated. The rearrangement then takes place in about a tenth part of the time required by boiling with water. This acceleration is in part at least to be attributed to the higher boiling point of the glacial acetic acid.

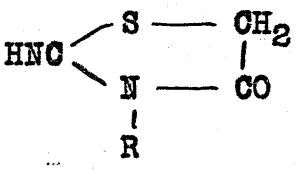
The Arylthiohydantoins are bases as well as acids. With hydrogenchloride they form crystalline salts which however are again dissociated by water. With sodium hydroxide they likewise form crystalline salts. From the sodium hydroxide compounds one can easily obtain alkylated arylthiohydantoins by the action of halogen alkyls, for example, the ethylnitrophenylthiohydantoin:



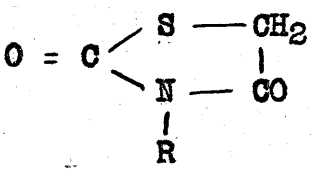
The sodium hydroxide compounds of the Arylthiohydantoins are formed by the simple addition of the components and have perhaps the following constitutional formula:



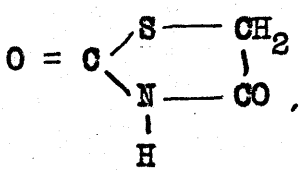
By prolonged heating with hydrochloric acid, preferably in a sealed tube, the imide group in the Arylthiohydantoins is replaced by oxygen. There result thus Arylderivatives of mustard oil glycolid,



Arylthiohydantoin

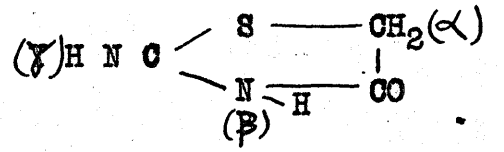


Arylmustard oil glycolid.

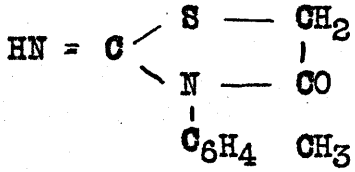


Mustard-oil glycolid.

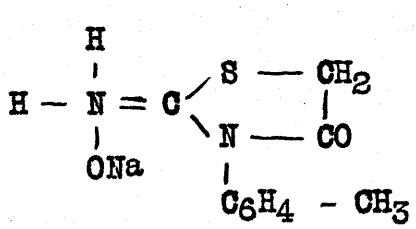
Up to the present, there has been little uniformity in the literature to the nomenclature of the substituted thiohydantoins. We have chosen as a foundation for the symbol of the compounds in general the scheme:



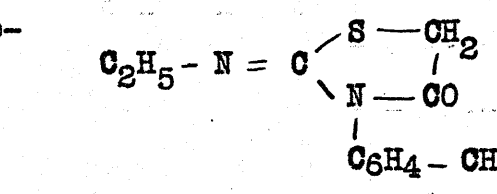
In this publication several series of compounds according to these workers are prepared and described. Members of the first series are listed below:

Name	Melting Point	Formula assigned
Chloracet-m-toluidide,	90-91° ,	$Cl - CH_2 - CO - NH - C_6H_4 - CH_3$,
Isothiocyanacet-m-toluidide,	99° ,	$SCN - CH_2 - CO - NH - C_6H_4 - CH_3$,
Thiocyanacet-m-toluidede,	136° ,	$NCS - CH_2 - CO - NH - C_6H_4 - CH_3$,
B-m-Tolylthiohydantoin,	161° ,	

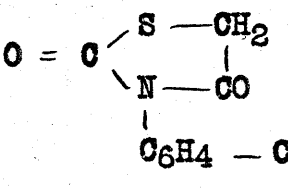
B-m-Tolylthiohydantoin sodium hydroxide:



Gamma-Ethyl-β-m-Tolylthio-hydantoin - An Oil ,



M-Tolylmustardoilglycolide, 90-91°.



This series was repeated, (with the exception that in some cases the isothiocyanacetanilide and the glycolide were not secured), with the following amines:

(a) Pseudocumidine: (the iso-compound and glycolide not obtained)

(b) Parachloraniline: (the iso-compound and glycolide obtained)

(c) Metachloraniline: (the iso-compound not secured)

(d) Orthonitroaniline: (" " " and glycolide not obtained)

(e) Metanitroaniline: (the iso-compound and glycolide not obtained)

(f) Paranitroaniline: (the iso-compound and glycolide not obtained)

(g) Nitrotoluidine: (the iso-compound and glycolide not reported)
[$CH_3 \cdot (1)\ NH_2 \cdot (4)\ NO_2 \cdot (3)$]

(h) Nitrotoluidine: (the iso-compound and glycolide not reported)
[$CH_3 \cdot (1) \cdot NH_2 \cdot (4) \cdot NO_2 \cdot (2)$]

(i) Nitrotoluidine: (the iso-compound and glycolide not reported)
[CH_3 (1) NH_2 (2) NO_2 (5)]

(j) Paraanisidine: (the iso-compound and glycolide not obtained)

(k) Orthoanisidine: (the iso-compound not obtained)

(l) Paraphenetidine: (the glycolide obtained) .

F. B. Dains and A. E. Stephenson[1] show that "the

(1) J. Am. Chem. Soc. 38, 1841-4 (1916).

CH_2-group of the -CO - CH_2 - S - complex of isothiohydantoins reacts with substituted formamidines like other CH_2 compounds, with formation of a primary amine and substitution of the complex >CH·NHR for the two H-atoms. Thus diphenylisothiohydantoin and Ph N : CH NHPh give Ph NH_2 and 2-phenylimido-3-phenyl-4-keto-5-anilinomethylenetetrahydrothiazole

Ph N : CO - C(: CHNHPh) S .

Hydrolysis of this gave the 2, 4-diketo derivative diphenylthiourea, phenyl-2, 4-diketotetrahydrothiazole and Aniline hydrochloride. The following compounds are also recorded:

(1) 2-o-Tolylimido-3-o-tolyl-4-keto-5-anilinomethylene-tetrahydrothiazole.

(2) 2-Phenylimido-4-keto-5-anilinomethylenetetrahydro-thiazole.

(3) 2-Methylphenylamino-4-keto-5-anilinomethylene-tetrahydrothiazole.

(4) 2, 4-Diketo-5-anilinomethylenetetrahydrothiazole.

* * * *

"On the reactions of the formamidines, VI. Some Thiazole Derivatives." --Dains and Stephenson.(1)

"It has been pointed out(2)

Compounds containing a methylene grouping react with ease with the substituted formamidines, giving a primary amine and the complex CHNHR in place of the

(1) Jr. Am. Chem. Soc. 38, 1841. Sept. 1916).

(2) Ber., 35, 3509 (1902): This Journal, 31, 1148 (1909) : 35, 959, 970 (1913).

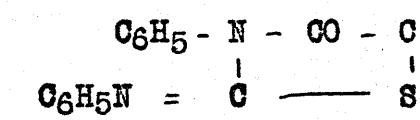
H_2 of the methylene group, as follows:

$$>CH_2 + RN = CHNHR = >C = CHNHR + RNH_2.$$

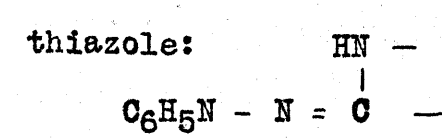
This occurs not only in the malonic ester, acetoacetic ester and benzylcyanide type, but also with ring compounds like pyrazolones and isoxazolones. In the isothiohydantoins (ketotetrahydro-thiazoles) there is found the complex $-CO-CH_2-S-$ which exhibits the general reactions characteristic of an acid methylene grouping, such as aldehyde, phthalic anhydride, nitroso derivatives, etc."

Compounds prepared:

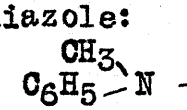
2-phenylimido-3-phenyl-4-keto-5-anilido-methylene-tetrahydrothiazole,



2-phenylimido-4-keto-5-anilidomethylene-tetrahydrothiazole:

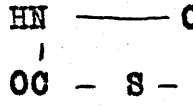


2-methyl-phenylamido-4-keto-5-anilido-methylene-tetrahydrothiazole:



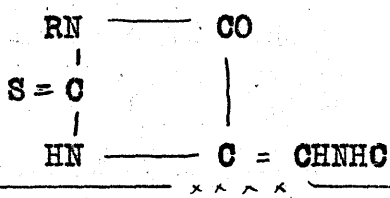
3-phenyl-2, 4-diketo-5-anilidomethylene-tetrahydrothiazole:

2, 4-diketo-5-anilido-methylene-tetrahydrothiazole



"As a matter of interest it may be noted here that the true thiohydantoins containing a methylene group condense with the formamidines giving substituted

amino methylene derivatives of the type,



F. B. Dains, R. C. Roberts, and R. O. Brewster,(1) "On the Action of Certain Acid Reagents on the Substituted Ureas and Thiazole."

"A continuation of an investigation begun several years ago on the reactivity of the anilido hydrogen in the oxygen and sulphur ureas and is a study of the effect of acyl reagent on the grouping -NH-CO(S)NH- or NH = C = NR, SR, in both open-chain and ring compounds."

Karl H. Stieger in the laboratory of Andreasch(2) completes the series of substituted rhodanines by describing the isoamyl series.

The following isothiohydantoins are mentioned in the discussion:

β.-m-Nitrobenzalisothiohydantoin, from the components in Na OH solution, and subsequent heating with glacial acetic acid (m.p. 260° with decomposition). The first product of the reaction is m-nitro-benzal-isothiohydantoic acid which loses water with acetic acid.

β-Methylene-3, 4-dihydroxybenzalisothiohydantoin, m.p. 215°. The same compounds may be prepared by the

(1) J. Am. Chem. Soc. 38, 131 (1916).
(2) Monatsh. 37, 635-58 (1916).

use of acetic acid and sodium ethylate.

Di-p-hydroxyphenylthiohydantoin. m.p. 236°.

Andreasch[1].

"The condensation of rhodanines and related ring systems with aldehydes is illustrated still further in this work."

3-Phenyl-5-p-aminobenzylidenerhodanine,

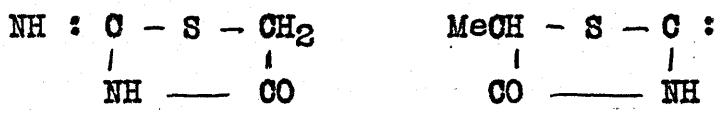
CO - NPh - CS - S - C : $CHC_6H_4NH_2$, is obtained from 3-phenylrhodanine and p-amino-benzaldehyde in warm glacial acetic acid.

2, 4-diketo-3-phenyl-5-p-aminobenzylidenethiazolidine,

CO - NPh - CO - S - C : $CH \cdot C_6H_4 \cdot NH_2$, is prepared.

Phenylthiohydantoin yields γ-phenyl-β-benzylidene-isothiohydantoin (2-imino-4-keto-3-phenyl-5-benzylidene-thiazolidine) and the corresponding salicylidene ecompound are prepared.

K. J. Lenander[2] prepared a thiohydantoin from thioacetic acid and cyanamide by the prodedure of Andreasch (Ber. 13, 1422).



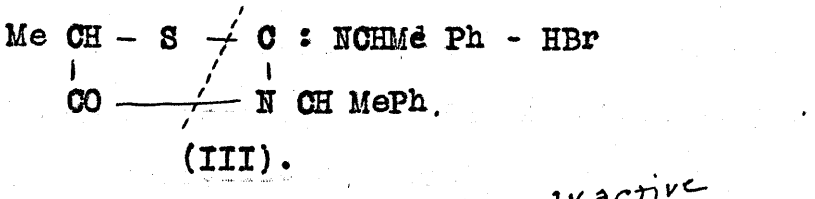
(I). (II).

Another thiohydantoin (II) was made from dyanamide and racemic thiolactic acid.

l-Diphenylethylthiocarbamide and dl-$MeCHBrCO_2H$

(1) Monatsh. 38, 121-39 (1917).
(2) C. A. 1917: (Svensk Kem. Tidskrift 29, 61-8 (1917).

yield (III) which on hydrolysis cleaves as indicated by the dotted line.



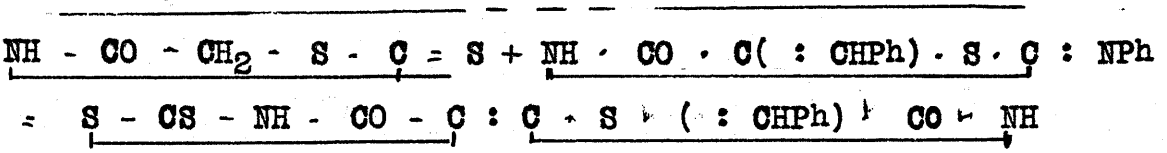
(III).

The compound (III) is an optically active substance and "its preparation was considered desirable from the point of view of fixing the constitution of this group of substances."

E. Schmidt(1), "assuming that the reaction whereby alkylated thioureas are changed into the corresponding guanidines through loss of S in NH_3 solution, could be extended to pseudothiohydantoin whereby a simple and convenient method would be available for the preparation of glycocamidine and its alkyl derivatives, found that the experiments attempted in this direction were not productive of the desired results."

A large amount of work on the true thiohydantoins of Johnson was encountered.

C. Gränacher(2).



from a publication on "Rhodanine."

E. Schmidt(3) observes that "the elimination of sulphur from ψ-thiohydantoin by means of mercuric

(1) Arch. Pharm. 256, 308-12 (1918).
(2) C. A. 1920, 1667: (Helvetica Chim. Acta 3, 152-63 (1920).
(3) Abs. Jr. Chem. Soc. (London) (1921). (Arch. Pharm., 1920, 258, 226-250.)

oxide (Volhard, Jr. Chem, Soc. London., 1873, 880: compare Maly, ibid., 1874, 684: Mulder, ibid., 1875, 446) is extremely slow, being incomplete even after four weeks at 100°. "Oxalic acid and ammonia were the sole products recognized. Glycocyamidene gives the same products under like treatment, hence the absence of this compound in the above experiment."

F. B. Dains, Roy Irwin, and C. G. Harrel[1] have published a paper on "Some Thiazolidone Derivatives" which is "a continuation of the earlier preliminary experiments in which it was shown that the complex $CO - CH_2 - S -$ in 4-thiazolidones exhibits the general properties of an acid CH_2 grouping, combining with the formamidines and yielding derivatives in which the methylene H is replaced by the aminomethylene complex:"

$$=CH_2 + RN : CHNHR \rightarrow =C : CHNHR + RNH_2.$$

The experiments described also show in somewhat greater detail that the 4-thiazolidones are characterized by the same reactivity of the methylene hydrogen towards benzaldehyde and the substituted formamidines.

The following compounds were prepared and characterized:

1. 2-m-tolylimino-3-m-tolyl-4-thiazolidone,
2. 2-p-bromophenylimino-3-p-bromophenyl-4- "
3. 2-phenylimino-3-p-bromophenyl-4-thiazolidone
4. 3-p-bromophenylimino-2, 4-thiazolidone

(1) J. Am. Chem. Soc. 43, 613-8 (1921).

5. 2-phenylimino-3-m-bromophenyl-4-thiazolidone
6. 3-p-chloro analog.
7. 2-m-nitrophenylimino-3-phenyl-4- "
8. 2-m-tolylimino-3-m-tolyl-5-benzal-4- "
9. p-tolyl isomer
10. 3-p-tolyl-5-benzal-2, 4-thiazolidone
11. 5-m-nitrobenzal analog.
12. 2-p-bromophenylimino-3-p-bromophenyl-5-benzal -4-thiazolidone
13. The chloroanalog.
14. 2-phenylimino-3-p-bromophenyl-5-benzal-4-thiazolidone
15. 3-m-bromo isomer
16. 2-m-nitrophenylimino-3-phenyl-5-benzal-4-thiazolidone
17. 2-p-tolylimino-3-p-tolyl-5-anilinomethylene -4-thiazolidone
18. 5-B-Napthylaminomethylene compound
19. 3-m-tolyl-5-anilinomethylene-2, 4-thiazolidone
20. 2-p-bromophenylimino-3-p-bromophenyl-5-napthylaminomethylene-4-thiazolidone ~~chloro analog.~~
21. Chloro analog.
22. 2-phenylimino-3-p-chlorophenyl-5-anilinomethylene -4-thiazolidone.

"The Reactions of the Formamidines VIII.

Some Thiazolidone Derivatives."

"In a previous paper, [Dains and Stevenson, This Jr. 38, 1841 (1916)] some preliminary experiments showed

that the complex - CO - CH_2 - S - in the 4-thiazolidones exhibited the general properties of an acid methylene grouping and combined with the formamidines yielding derivatives in which the methylene hydrogen was replaced by the aminomethylene complex,

$$>CH_2 + RN \cdot CHNHR = >C=CHNHR + RNH_2 \text{''}.$$

[Experiments in this paper extended and similar results obtained]

Preps:[1]

2-m-tolylimino-3-m-tolyl-4-thiazolidone

2-p- " " -3p- " " "

3-p-Tolyl-2, 4-thiazolidione

2-p-Bromo-phenylimino-3-p-bromophenyl-4-thiazolidone

2-p-chloro-phenyl-imino-3-pchlorophenyl-4-thiazolidone.

"When a thiourea of the type RNHCSNHR' is heated with chloroacetic acid, it is evident that 2 isomeric products may result.

$$RNHCSNHR' + Cl \cdot CH_2 \cdot COOH = \begin{matrix} RNH \\ RNH \end{matrix}\!\!>\!C = S\!<\!\begin{matrix} Cl \\ CH_2 \cdot COOH \end{matrix} =$$

$$\begin{matrix} R - N & \text{———} & CO \\ | & & | \\ R'N = C & - S - & CH_2 \end{matrix} \quad \text{or} \quad \begin{matrix} R' - N & \text{———} & CO \\ | & & | \\ RN = C & - S - & CH_2 \end{matrix} + HCl .$$

That there seems to be a selective action is shown [Dains, This Jr. 28, 1183 (1906); Dains, Roberts, Brewster, ibid, 38, 137 (1916)] by the fact that thus far only one of the possible isomers has been isolated. The conditions which control the choice are under investigation and it is hoped that enough experimental evidence can be obtained to throw light upon the reaction."

Preps:

2-phenylimino-3-p-bromophenyl-4-thiazolidone

3-para bromophenyl-2, 4-thiazoledione

2-Phenylimino-3-m-bromophenyl-4-thiazolidone

2-Phenylimino-3-p-chlorophenyl-4-thiazolidone

3-Para chlorophenyl-2, 4-thiazolidione

2-m-Nitrophenyl-imino-3-phenyl-4- "

5. Benzal Derivatives:

2-m-tolylimino-3-m-tolyl-5-benzal
-4-thiazolidone

2-p-tolylimino-3-p-tolyl "

2-p-Bromophenyl-imino-3-p-bromophenyl-5-benzal

2-p-chloro- " "

2-phenylimino-3-p-bromophenyl-5- etc.

2 " -3-m " -5- etc.

2-m-Nitrophenyl-imino-3-phenyl-5- etc.

II. Condensation Reactions with substituted formamidines.

6- condensations with the disubstituted compound are recorded.

Summary:

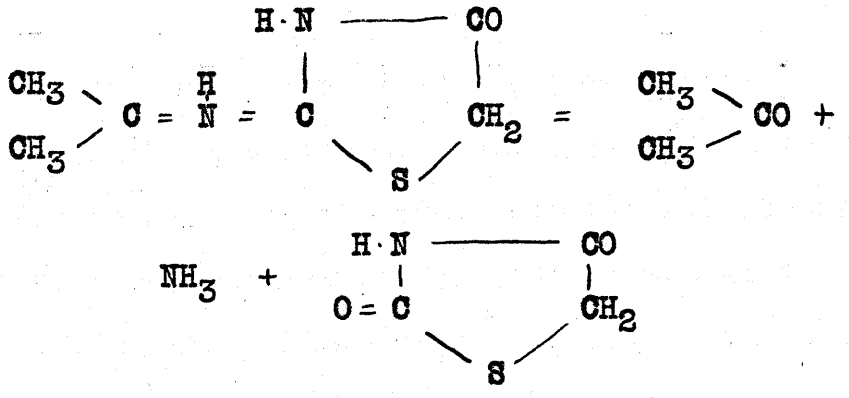
"A number of new disubstituted 4-thiazolidones and their benzal derivatives have been prepared containing either the same or different groups at positions 2 and 3.

The methylene group in these 4-thiazolidones has been found to react with the substituted formamidines giving derivatives of the type, $RN - CO$ / $RN = C - S - C = CHNHR'$.

Wilson and Robert Burns[1] found that "the action of l-menthylchloroacetate or of chloracetic ester upon Acetone thio-semicarbazone sodium derivative, $C_4H_8N_3S$ Na, gives a new type of ψ-thiohydantoinderivative

$$Me_2\,C : NH : \underline{C - NH - CO - CH_2 - S}$$

Hydrolysis gave acetone and 2, 4-diketo-tetrahydro-thiazole, thus indicating its constitution."



(My own observation)

This is of interest in showing the possibility of the imide nitrogen of thiohydantoin exercising a valence of five, a view conceived by Beckurts and Frehrichs in connection with the sodium hydroxide salts, of this class of compounds.

Wilhelm Wudich[2], in his work on the constitution of the so-called "β. dimethylisothiohydantoin" refers to the preparation of this compound by Andreasch[3] by the action of methyl iodide in methyl alcohol on the silver salt of isothiohydantoin and which he termed β. dimethylisothiohydantoin. Repetition of the work

(1) Jr. Chem. Soc. 121, 870-6 (1922).
(2) Monatsh, 44, 83-9 (1923).
(3) Monatsh, 8, 420.

shows that the silver salt could not be obtained pure but that it probably contained two atoms of silver. The methylderivative was obtained and is considered to be methylthioglycolylisomethylurea because on hydrolysis with hydrochloric acid at 150° in a sealed tube, NH_3 is split off and methyl-thioglycollic acid is formed (isolated as the barium salt).

Leon. Gendelman[1] in a paper entitled "Aldehyde Derivatives of Rhodamines and Their Fission Products" mentions the fact that β-p-chlorobenzal-thiohydantoin sinters at 230° but doesnot melt.

Dains and Miller[2], in a study of the constitution of the Mono-substituted thiazolidones prepared the following compounds:

2-phenyl-methyl amino thiazolidone
2-phenyl-imino-5-benzal "
2-phenyl-methyl-amino-5-benzal "
2-phenyl-imino-3-methyl "
2-phenyl-imino-3-methyl-5-benzal "
2-phenyl-ethyl-amino "
2-phenyl-ethyl-amino-5-benzal "
2-phenyl-imino-3-ethyl-5-benzal "
2-butyl-phenyl-amino "
2-phenyl-imino-3-butyl "
2-phenyl-acetyl-amino "

(1) Monatsh., 43, 537-43 (1923).
(2) Thesis: K. W. U. 1925.

2-phenyl acetyl-4 (?) acetyl thiazolidone.

These $\alpha\alpha$ disubstituted products were made from the corresponding assymetrical disubstituted thioureas and chloraceticester. Hydrolytic products are not recorded.

R. M. Hann and K. S. Markley[1] on the "Condensation of Aldehydes with Diphenylisothiohydantoin" prepared 2-phenylimino-3-phenyl-4-thiazolidone which contains the reactive group, $-S-CH_2-CO-$ for use in their experiments. They prepared aldehyde condensation products with it from o-hydroxybenzaldehyde, chloro-vanillin, benzaldehyde, o-nitrobenzaldehyde, cynnamyl-aldehyde, furfural, 3, 5, 2-dichlorhydroxybenzaldehyde, 3,4-dihydroxy-benzaldehyde and several others.

A new method of ascertaining the condition of peptides is reported by Schlack and Kumph.[2]

"The ease with which an amino acid or the terminal amino acid grouping of an acylated di- or tripeptide may be converted into the thiohydantoin ring by treatment with NH_4SCN and AC_2O, and the thiohydantoin then split off by hydrolysis with alkali, furnishes a new method of attack in studying the constitution of peptide chains. The thiohydantoin thus liberated is readily isolated and identified."

B. H. Nicolet and F. Bate[3] report that the follow ig

(1) J. Wash. Acad. Sci. 16, 169-75 (1926).
(2) Z. physiol. Chem. 154, 125-70 (1926).
(3) J. Am. Chem. Soc. 49, 2064-6 (1927).

pseudothiohydantoins were prepared from the α-Br acid and $(H_2N)_2CS$; 5-butyl, 5-decyl, 5-duodecyl, 5-duodecyl, 5-tetradecyl, 5-hexadecyl.

"These show little or no m.p. depression when mixed and thus presumably form solid solns. to an unusual extent. They are of no value for the sepn. or identification of the higher fatty acids. Hydrolysis of these compounds gives the following α-mercapto acids: caproic, lauric, myristic, palmitic, stearic, lauric acid α-disulphide, α-Carboxyamylsulfonic acid, analyzed as the Ba salt."

Ben H. Nicolet and Langston Fairchild Bate(1) report that α-Halogeno derivatives of the simpler fatty acids or their esters condense readily with thio-urea to give 5-substituted pseudo-thiohydantoins. "Acids of longer chain than butyric do not seem to have been used for this reaction, and it was thought worth while to extend it to some of the higher homologs, primarily with the hope that the derivatives might be of service in the separation or identification of the higher fatty acids."

"Caproic, lauric, myristic, palmitic, and stearic acids were converted by standard methods into the α bromo acids or esters (these react equally well). When the products, dissolved in five parts of alcohol, were warmed for an hour on the water-bath with slightly more than one molecular equivalent of thio-urea,

(1) Journ. Am. Chem. Soc. Aug. 1927.

practically quantitative yields of the crude pseudo-thiohydantoins were, obtained. Several crystallizations from alcohol were usually necessary before a constant melting point was reached. ---------"

--------- Summary.

1. The pseudo-thiohydantoins corresponding to caproic, lauric, myristic, palmitic, and stearic acids have been described, together with the ∝ mercapto acids obtained from them by hydrolysis
2. The pseudo-thiohydantoins, while easily obtainable, offer no promise as derivatives for the separation or identification of the higher fatty acids."

Dains and Holmberg[1] in further researches on the constitution of the monosubstituted thiazolidones prepared and described the following compounds:

2-p-tolyl-4-thiazolidone and its sodium salt

2-p-tolyl-2-ethyl-amino-4-thiazolidone

∝-ethyl ϒ- p-tolyl-B-phenyl urea

2-p-tolyl-2-benzyl-amino-4-thiazolidone

∝-benzyl ∝- p-tolyl B-phenyl urea

2-p-tolyl-2-p-nitrobenzyl-amino-4-thiazolidone

p-nitro benzyl-p-toluidine

2-p-tolyl-2-ethyl-amino-5-benzal-4-thiazolidone.

2-4-di keto-5-benzal thiazolidone

5-benzal-4-thiazolidone

(1) Thesis K. U. 1927.

∝ -p-tolyl-3-ethyl-4-thiazolidone

3-ethyl-2-4-di-keto-thiazolidone

2-p-tolyl-3-ethyl-5-benzal-4-thiazolidone

2-p-tolyl-3-ethyl-5-benzal-4-thiazolidone

2-p-tolyl-4-thiazolidone

Monochloracet-p-toluidine

Sodium salt of 2-p-tolyl-4-thiazolidone

2-p-tolyl-2-benzal-amino-4-thiazolidone

HCl- salt of 2-p-tolyl-2-benzal-amino-4-thiazolidone

2-p-tolyl-2-ethyl-amino-4-thiazolidone

∝-p-tolyl ∝ benzyl-B-phenyl urea

HCl salt of 2-o-tolyl-2-ethyl-amino-4-thiazolidone

∝-o-tolyl ∝-ethyl B phenyl urea

2-o-tolyl-2-methyl-amino-4-thiazolidone

∝-o-tolyl ∝-methyl-B-phenyl urea

2-p-anisidine-4-thiazolidone

Monochlor acetyl p-anisidine

Sodium salt of 2-p-anisidin-4-thiazolidone

2-p-anisidin-2-ethyl-amino-4-thiazolidone

2-p-anisidin-2-benzyl-amino-4-thiazolidone

Kingsbury and Markley[1] prepared diphenyl-thiohydantoin by refluxing diphenyl thiourea and chloracetic acid in alcohol for three hours.

The following 2, 3-diphenylisothiohydantoins were prepared by condensing this with aldehydes,

(1) Jr. Wash. Acad. Sci. 18, 558-61 (1928).

5-o-methyoxybenzal-2, 3-diphenylisothiohydantoin

5-anisal "

5-veratral "

5-piperonal "

5-p-tolual "

5-p-hydroxybenzal "

5-o-chlorobenzal "

5-m-nitrobenzal "

5-citral "

Rudolf Andreasch[1] on Rhodanines and Related Compounds" reports that in the reduction of benzalphenyl-rhodanine, the S of the thioketo group is replaced by H_2, giving, 4-keto-3-phenyl-5-benzaltetrahydro-thiazole, (m.p. 206°). In a similar manner 4-keto-3-phenyl tetrahydrothiazole (m.p. 115°) and the 3-p-tolyl derivative, (m.p. 143°) were prepared.

The reduction product of rhodanine is apparently hydrolyzed during the concentration of the reaction product, thioacetic acid, $HSCH_2$ COOH, being isolated.

Diphenylthiohydantoin and benzaldehyde in glacial acetic acid give 85% of benzaldiphenylthiohydantoin (m.p. 206°). Attempted reduction leads only to the splitting off of aniline.

H. W. Stephen and Forsyth J. Wilson[2], with reference to the so-called bisthiohydantoins of

(1) C. A. (1929) : Monatsh, 49, 122-32 (1928).
(2) Jr. Chem. Soc. 1928, 2827-7: of C. A. 4, 2294: 7, 3476.

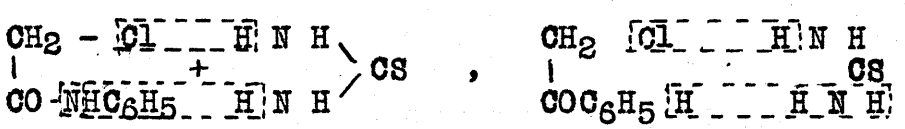
Frerichs, Förster and Höller, claim that it "has been shown (C. A. 22, 3410) that the so-called 3, 3-bis-ψ-thiohydantoin is really diketotetrahydrothiazole-2-ketazine. It is now shown that the two compounds described by F. and F. and by F. and H. are similar in structure. $H_2NCSNHNHCSNH_2$ and Et·CHBr CO_2 H give 2, 4-diketo-5-methyltetrahydrothiazole-2-ketazine (m.p. 289°) ; hydrolysis yields N_2 H_4 and 2, 4-diketo-5-methyltetrahydrothiazole, (m.p. 46-7°). The corresponding 5-Et-derivative (m.p. 233°) behaves similarly on hydrolysis."

H I S T O R I C A L S U M M A R Y

On page 1965, volume X of the Berichte der Deutschen Chemischen Gesellschaft, there is an article of Paul J. Meyer entitled, "Concerning the Substituted Sulpho-Hydantoins". In this article, which was published in the year 1877, he states, in part:

"If equivalent amounts of chloracetanilide and thiourea, dissolved in alcohol, be heated for some time on the water-bath, there separates a rich crop of crystals, which when filtered from the cooled solution and recrystallized from hot water or alcohol, prove to be Sulpho-hydantoin. From the filtrate, which contains ammonium chloride and the hydrochloride of aniline a voluminous precipitate is obtained by treatment with water, which after repeated crystallization from alcohol is established by analysis as phenylthiohydantoin."

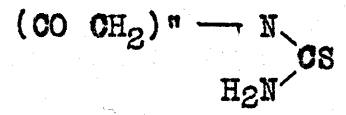
His conception of the formation of the two bodies is represented graphically as follows:



He states further that "the same body", namely, the substituted product, "is also produced when phenyl-thiourea is heated with monochloraceticester in alcoholic solution." Also, the tolyl derivative "is obtained in

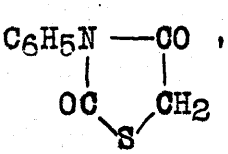
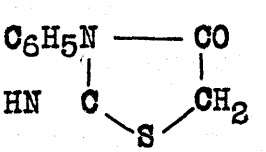
a similar manner from chloracettoluidide and thiourea along with sulphohy-dantoin."

He remarks that "the existance and formation of these two bodies", namely the substituted, and the unsubstituted hydantoins, "can only with difficulty be made to agree with the newly announced hypothesis of Maly (B.X, 1853) concerning the constitution of the thiohydantoins;

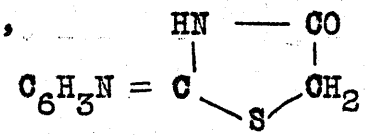


, which would assume a complete molecular rearrangement and would scarcely suffice to explain the formation of a second isomeric phenyl-sulpho-hydantoin which appears to form by melting together phenyl glycocoll and thiourea."

Since the time of the publication of the above article a great deal of work has been done by various investigators with the view to determine the constitution of the substituted thiohydantoins.

Paul J. Meyer in his work with the mono phenyl derivative found that it gave on heating with hydrochloric acid, 2-4 diketo, 3 phenyl-thiazolidone,  , and concluded that the original product had the constitution indicated by the following formula:  .

Liebermann and Lange, and Andreasch also adopted this view, although the former authors seem to have

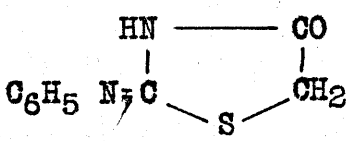
suggested the possibility of the isomer represented by the formula,  , a view which was later favored by Neubert, Goldschmidt and Gessner, although these submit no experimental evidences for their views.

The works of Dixon, (1877), seems to present the first evidence in favor of the latter formula. He reasoned that a compound of the 3 phenyl type when treated with carbon bisulphide should yield thiocyanic acid while the isomeric 2-phenyl derivative should give phenyl thiocarbimide. His conclusion was that the latter reaction took place, a fact which appears to show that the phenyl group may be attached to the doubl binded nitrogen. This however left unexplained the formation of the diketo compound by boiling the phenyl derivative with hydrochloric acid, and the formation of the unsubstituted compound from thiourea and chloracetanilide.

Wheeler and Johnson found that phenylpseudo-thiohydantoin behaves tautomerically and suggested a similar behavior for the phenylthiohydantoins. They prepared normal thio-cyanacetanilide, melting point at 91°, by warming potassium thiocyanate and chloracetanilide in strong alcohol. This product when melted in the dry state on the steam bath for fifteen minutes is converted into an isomer melting at 148°. This they

claimed to be the 3 phenyl derivative. When heated for a longer period, or, at a higher temperature, it is converted into the stable form melting at 178°.

They found further that unsymmetrical benzyl-phenyl-thiourea and ethyl chloracetate give thesame product which is produced by the interaction of the stable phenyl thio hydantoin and benzyl chloride in alkaline solution. This shows that the phenyl group is attached to the nitrogen outside the ring but leaves unsettled the position of the hydrogen replaced by the benzyl group. They concluded that the most probably structure of the phenyl derivative of thio hydantoih is that assigned by Dixon, namely,



The results of the work of Beckurts and Frerichs however, was such as might lead one to believe that the 2-phenyl type does not exist. They prepared what they claim to be the 3-meta-tolyl derivative, the sodium salt of which on treating with ethyl iodide gave the 2-ethyl-3-m-tolyl compound. A number of similar compounds were prepared by varying the aryl groups. They found that on hydrolysis of the monosubstituted products they obtained, in a number of cases, the corresponding diketo derivatives, the aryl groups remaining attached to the ring. On these grounds it appears they assume for the disubstituted products the general structure,

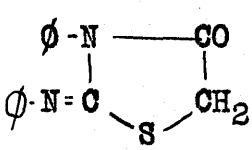
an assumption which, we believe, from the results of our work, not to be warranted.

Our examination of the literature as recorded in the preceeding pages, seems to reveal, that, at the present time there is no general agreement as to the structure of the isothiohydantoins. The form assigned to monophenyliso thiohydantoin by Meyer and others early in the history of the subject seems to be supported by the work of Beckurts and Frerichs in 1915.

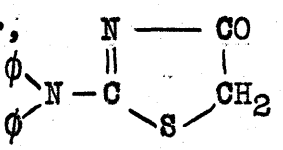
The formula of Dixon and others, on the other hand, appears to find confirmation in the work of Wheeler and Johnson, and others. The recognition of both forms by the latter authors, described by them as the labile and stable forms seems to be in conflict with the view of Beckurts and Frerichs.

The constitution of the disubstituted isothiohydantoins is still no less a matter of controversy. In cases where the substituent groups are identical there can be less disaggreement than in those cases where the two groups are not the same.

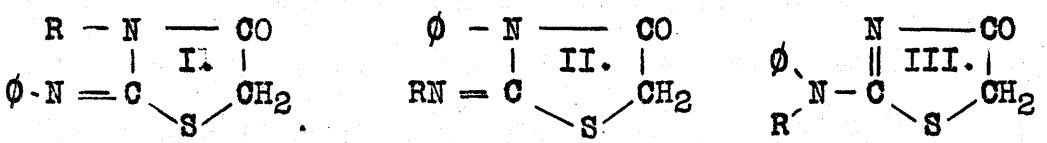
Thus for diphenylisothiohydantoin the structure,



, appears to agree well with the facts of experiment, namely the mode of formation and the products

of hydrolysis. However, the isomer,  ,

can be prepared by other methods which would indicate the structure assigned. However the possibility of the existance of both isomers in any preparation from whatever method apparently has not been demonstrated. As to the structure of disubstituted isothiohydantoins where the groups differ there is room for even greater uncertainty. For in such cases there is the possibility of three isomeric forms.



The type represented by formula (III) has been prepared, the structure, in some instances having been inferred from the mode of formation, in others, seemingly confirmed by the facts of hydrolysis.

However, when the form (I) and (II) are considered the question arises as to the relative positions of the two groups ϕ and R. Experimental results appear to point to a preference for the form in which the more positive of the groups is attached to the imide-nitrogen. However, the non-existance of the isomer in which the more positive group is attached to the ring nitrogen, has not, I believe, been demonstrated. The possibility of the existance of such isomers in admixture from any method of preparation might be expected. In cases where the two groups exhibit a considerable difference in acidity one might expect to find the tendency to

shift less pronounced. In such cases the possibility of identifying the isomers is worthy of consideration. The existance of isomers in admixture from preparations which theoretically should give products with the two substitutive groups on difference nitrogen, I believe, has not been demonstrated, nor so far as I have been able to find in the literature, has this possibility been fostered(?). (See Dixon).

In the work for this thesis it has been clearly demonstrated in two cases and strongly suspected in others, that when a disubstituted isothiazolidone is prepared by a method which theoretically should give the $\alpha\alpha$-product, not only this product results but also, at least one isomer in which the two groups occur on different nitrogen atoms.

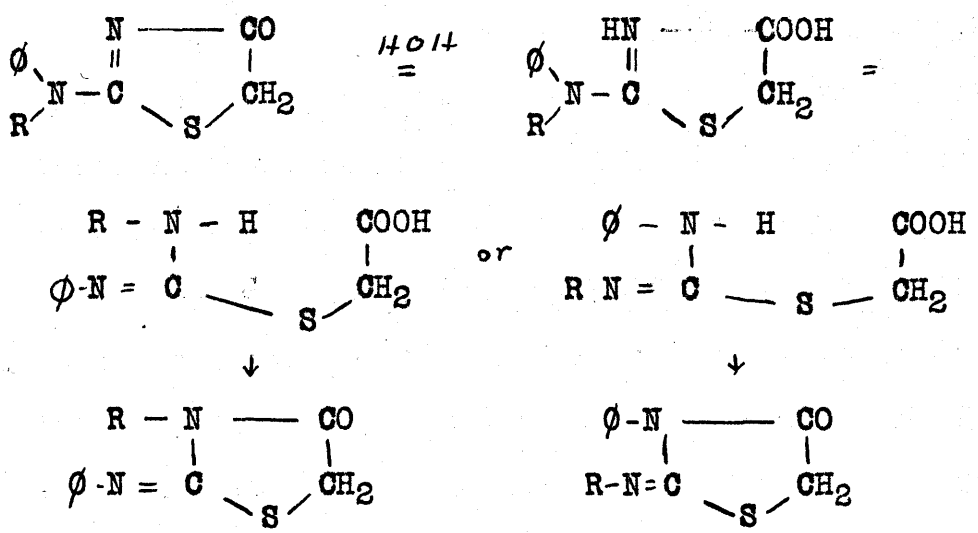
The relative positions of the groups in these cases, however, are yet to be shown, and work along this line is contemplated.

These isomers have actually been separated from each other and examined, which, we believe is the first time in the history of isothiohydantoins that this has been accomplished. In one case three substances, differing in melting points (and in superficial appearance) but of the same nitrogen content, were isolated from a mixture. The possibility of the actual existance of the third theoretically possible isomer is thus strongly suspected yet not satisfactorily demonstrated because of the fact that

the quantity of this substance isolated was insufficient for examination other than for nitrogen content, melting point and physical appearance.

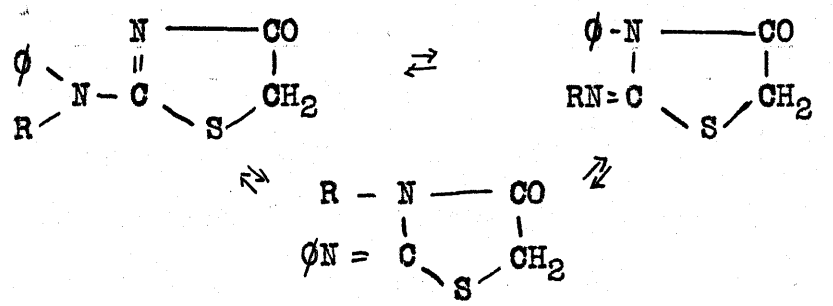
The question now naturally arises, ~~If~~ as to the possibility~~ies~~ of the existance of isomers in preparations by methods which would theoretically admit of but one type. On the other hand it is conceivable that such methods owing to the reaction of the medium (neutral or acid) might yield only the expected type of compound while the method used by us involving as it does at least a slightly alkaline medium might bring about a temporary splitting of the thiohydantoin ring with subsequent rearrangement and reclosing of the ring.

From the mode of formation of the α-compound and from the fact of the existance of isomers in the reaction mixture, the conclusion must be drawn that a shift of one of the substitution groups is involved:



Or possibily the following condition exists in an

alkaline solution:



Hydrolysis of such mixtures in acid solution might be expected to yield a primary, or a secondary amine or a mixture of the two types depending upon the rate of equillibrium shift, in the system.

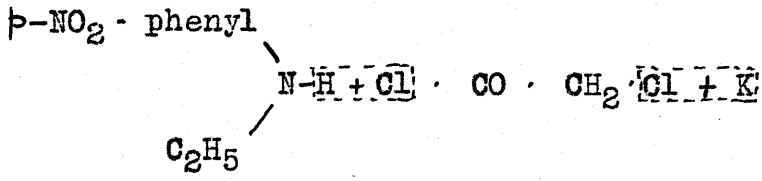
Dixon thought of the possibility of obtaining the isomerides by the interaction of allylphenylthiocarbamide and chloracetamide. He states that the oil obtained was subjected to hydrolysis with dilute HCl : that "the solution reacted strongly for aniline and when heated with excess of potash, freely evolved an alkaline gas having a pungent ammoniacal odour, but giving with Nessler's solution a pale primrose-yellow precipitate, and hence consisting, not of ammonia, but of allylamine. From the above results it would appear that the oil contains both the expected isomeric forms, although, in this instance, they could not, be isolated."

In this connection, attention should be called to the observation(1) that "When a thiourea of the type RNHCSNHR' is heated with chloracetic acid, it is evident that two isomeric products may result. That

(1) Dains, Irwin, and Harrel: Jr. Am Chem. Soc. 43, 614-615.

there seems to be a selective action is shown[2] by the fact that thus far only one of the possible isomers has been isolated."

The possibility of the existance of a third isomer is not mentioned. An investigation in this direction is contemplated. For instance, in the preparation of a certain disubstituted isothiohydantoin, by a method which theoretically should produce it along, two isomers and possibly a third have been shown to be present. It would seem likely that these isomers might be present in a preparation made, for example, from symmetrical p-nitrophenyl-ethyl thiourea and chloracetic-ester, or, for that matter, in one made from α-p-nitro-phenyl-ethylthiourea and the ester, or, perhaps, in that resulting from the interaction of p-nitro-phenyl-ethyl amine and chloracetychloride and potassium thiocyanate.



The present paper contains some work with reference to this last item.

The work which was started in the summer of 1927,

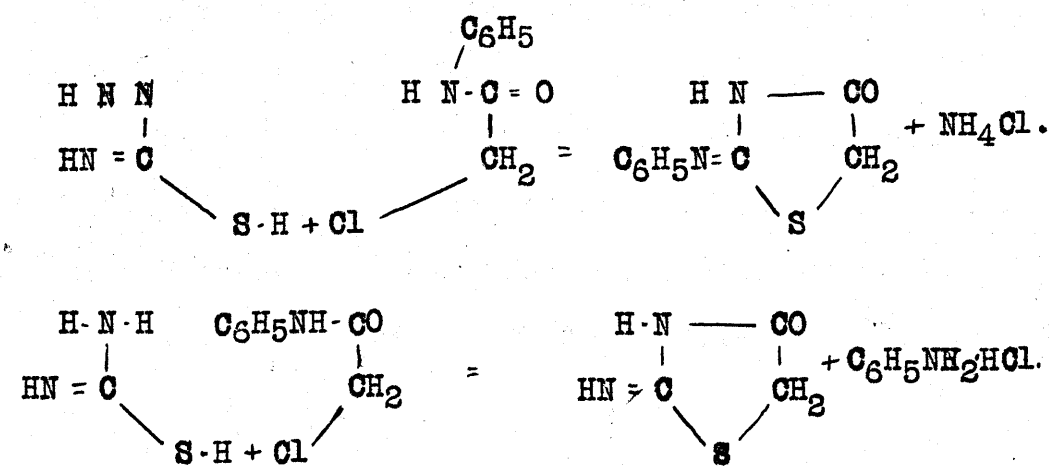
(2) Dains: J. Am. Chem. Soc. 28, 1183 (1906);
Dains, Roberts, Brewster, ibid., 38, 137 (1916).

with the hope of throwing additional light on the constitution of the isothiohydantoins, is recorded in the pages immediately following.

E X P E R I M E N T A L : S U M M A R Y

In the method used by Meyers, it will be recalled, two compounds were obtained. The possibility of controlling the reaction by a proper choice of solvent and neutralizing agent was suggested. Work along this line by Dr. Daiss had already given evidence of favorable results. At his suggestion then, experiments were started with the view of synthesizing certain thiohydantoins using acetone as solvent in place of alcohol, both in the presence of and in the absence of pyridene as a neutralizing agent. The hope was to develop a method which would insure the production of a definite type of compound.

As previously stated, Meyer obtained thiohydantoin and its phenyl derivative by heating thiourea and chloracetanilide in alcoholic solution.



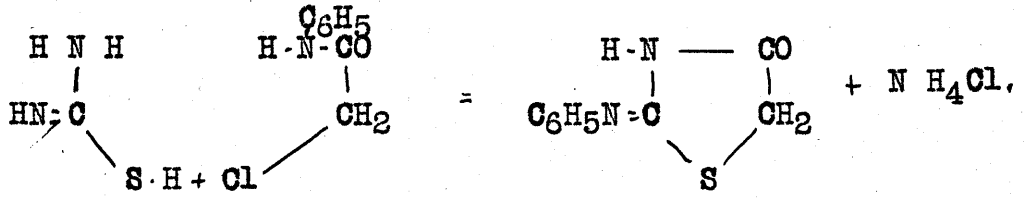
In order to determine the course of the reaction when acetone is used as a solvent, chloracetanilide,

20 gms. thiourea, 10 gms. and dry acetone, 60cc. were placed in a flask supplied with a reflux condenser. On standing for an hour without heating, the solid material, with the exception of a portion of the thioureas, had gone into ~~the~~ solution. On refluxing over boiling water for a half-hour, a heavy liquid separated. The acetone was removed by distillation on a water bath and the residue allowed to cool, with resultant partial crystallization. On adding cold water and agitating, a mass of pale-yellow crystals remained. These were filtered off and the filtrate made to volume for subsequent analysis.

The crystals dissolve in warm alkali and are reprecipitated white. The melting point corresponds to that of phenyl thiohydantoin. Some of the filtrate on evaporation leaves a syrup which, when stirred up with alcohol, yields a white solid. This product, from hot water, judging from its melting point, is also the phenyl derivative.

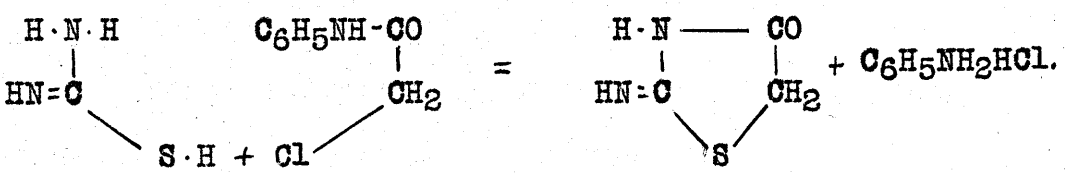
The filtrate gave a positive test for ammonia and a negative test for aniline.

An aliquot portion of the filtrate, made alkaline and distilled, gave an amount of ammonia such as would indicate that the main reaction was in the direction of the formation of the phenyl derivative of thiohydantoin.



The above experiment was repeated, one mole of pyridine being used.

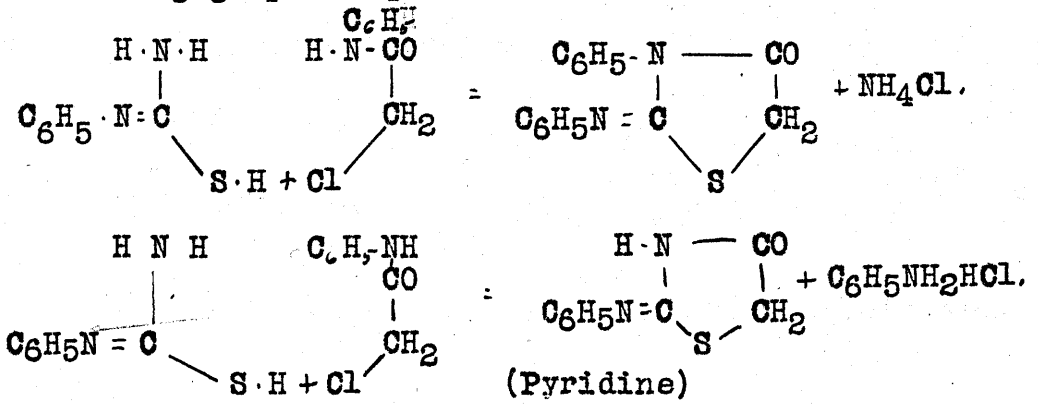
The crystals which separated during the period of digestion, after recrystallizing from hot water, melted with decomposition at 220°, the melting point of thiohydantoin. Several grams of aniline were obtained from the filtrate.



These experiments were repeated a number of times with the same general results.

It might be inferred then that the removal of hydrogen chloride from the reaction mixture by the pyridine favors the type of reaction which involves the removal of nitrogen from the chloracetanilide, whereas in the absence of pyridine a nitrogen from thiourea is lost.

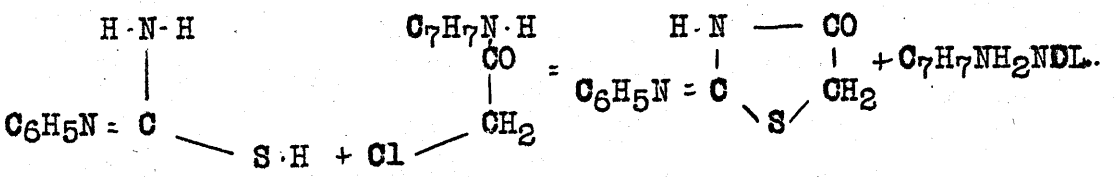
If these effects are general it would seem that if phenyl thiourea were substituted for thiourea in the above experiments, a diphenyl thiohydantoin should be obtained in the absence of pyridine, and a mono phenyl derivative in its presence, in accordance with the following graphic equation:



It was found however that both with and without pyridine the mono phenyl derivative alone was obtained. Thus the product anticipated was obtained only in the case where pyridine was used. The theory that the nitrogen of the thiourea derivative should be lost in the absence of pyridine was not substantiated.

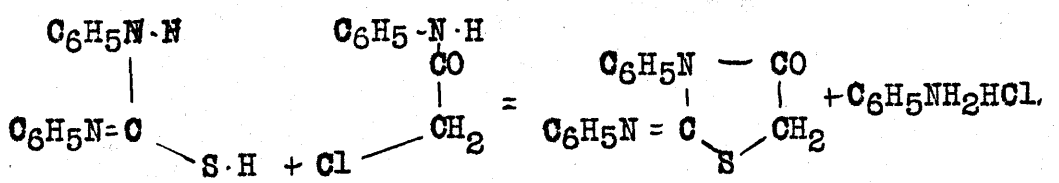
The question was then suggested as to the interaction of phenyl thiourea and chloracetotoluidide. Would they condense with loss of thiourea nitrogen or toluidide nitrogen?

Molar quantities were treated in acetone in the absence of pyridine, in the manner previously described. Mono phenyl thiohydantoin and toluidine were obtained, showing that the reaction had taken place in accordance with the following equation:



Again the result was contrary to the original theory.

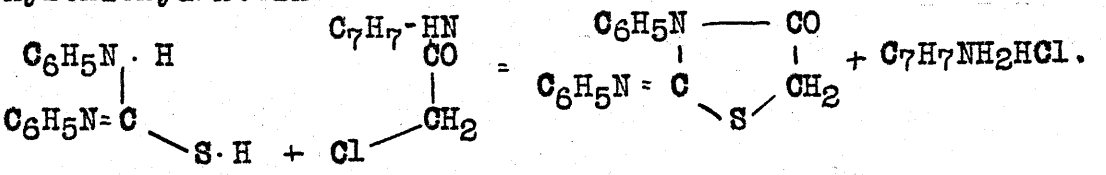
Molar quantities of diphenylthiourea and chloracetanilide with and without pyridine were next tried out. In each case a product was obtained which, by melting point tests, corresponded to diphenyl-thiohydantoin.



Chloracetylbenzylamine and thiourea, a mole each

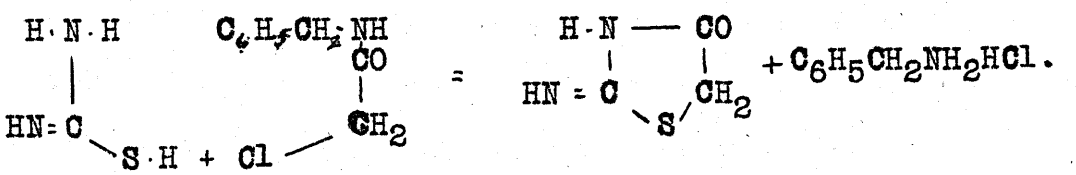
in alcoholic solution, gave a product melting with decomposition at 220°, which is evidently the unsubstituted thiohydantoin.

Chloracettoluidide and diphenylthiourea on similar treatment gave, in part at least, the diphenylthiohydantoin:



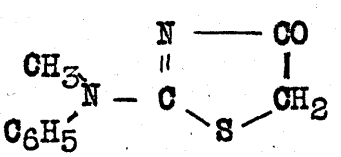
Chloracetylbenzylamine and thiourea, a mole each, in alcoholic solution, gave a product melting with decomposition at 220 degrees centigrade.

The same materials in acetone both with and without pyridine in each case gave the same product melting at 220°.



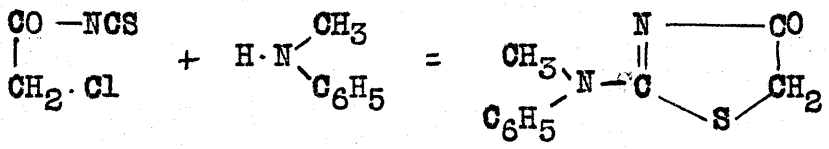
It would thus appear that, under the conditions of the experiment, namely, refluxing over boiling water, the tendency to condense with the elimination of the nitrogen of the chloro compound predominates.

The compound, methyl-phenyl thiohydantoin,



is a representative of the class of thiohydantoins

having two substituting radicals attached to a single nitrogen atom. It was made by Dixon from methyl phenyl amine and chloro-acidthiocarbamide as shown by the following equation:



Acting upon this suggestion, the question arose as to what would be the outcome if a secondary amine were treated with thiocyanoacetyl chloride, $\begin{matrix} CO\text{-}Cl \\ | \\ CH_2NCS \end{matrix}$.

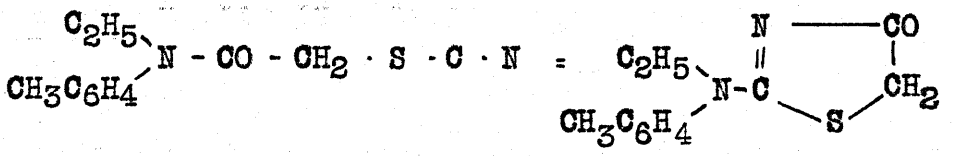
Orthotoluidine and diethylsulphate gave o-tolyl-ethyl-amine.

O-tolylethylamine and chloracetylchloride gave an oil which is doubtless the o-tolylethylamide of chloroacetic acid.

This product with KSCN gave a thick heavy dark oil which had the same consistency and appearance as the o-tolyl-ethyl thiohydantoin prepared from the sodium salt of o-tolylthiohydantoin and ethyl iodide. Hydrolysis gave o-tolylethylamine and a product whose analysis corresponded to the o-tolylethylamide of thioacetic acid. It is a question whether this product is the hydantoin however because of the difficulty of obtaining a good nitrogen determination. In this determination the distillate continues alkaline until quite an abnormal amount has been collected, whereas the hydantoin prepared from the salt

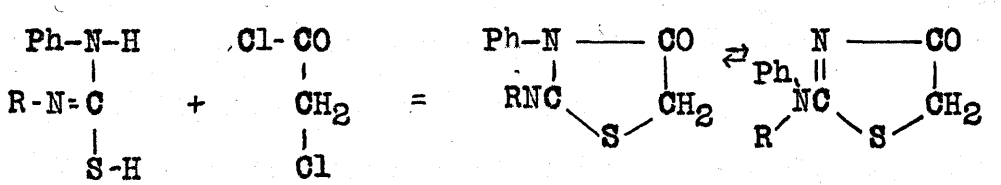
and the iodide behaves normally.

If ring closure should take place as indicated graphically below,

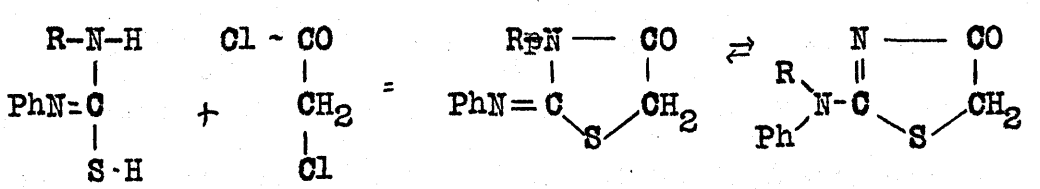


this would mean, that both substituting groups pass from the amide nitrogen to that of the thiocyanate group. This fact, if it be a fact, taken in conjunction with the evidence, supplied ~~in~~ later, that certain ethyl-aryl substituted thiohydantoins have a like structure, suggested the possibility that the alkyl-aryl disubstituted thiohydantoins in general, prepared in whatever manner, might have such a structure. If so, then alkyl-aryl disubstituted thiohydantoins prepared by the routes indicated below should have the same structure:

I. $2Ph.NH_2 + CS_2 = Ph-N-H / PhN=C-SH = Ph-N \| C=S + H_2N-R$



II. $R-NH_2 + CS_2 = R-N-H / R N=C-SH = R-N \| C=S + H_2N-Ph.$



Not having an alkyl amine available at the time, two aryl amines, aniline and o-toluidine, were used with the view of finding out what would happen when the reactions are carried out in the manner indicated above.

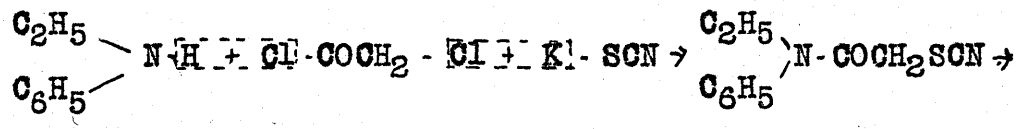
Both of the di-aryl thioureas obtained appear to be identical in certain physical properties, as also do the corresponding thiohydantoins. These two compounds were analyzed and subjected to hydrolysis, in an endeavor to determine whether they differ in structure.

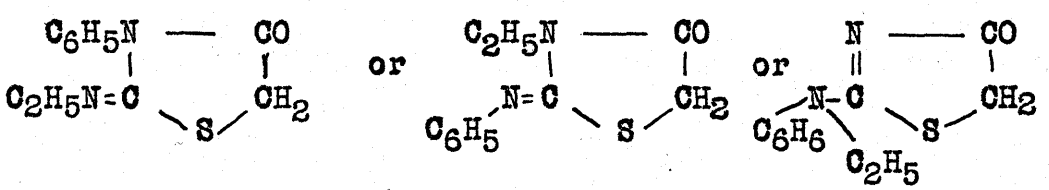
It was found that the thiohydantoin prepared from o-tolyl mustard oil, aniline and chloroacetyl-chloride is identical with that prepared by way of phenyl mustard oil, o-toluidine and the acid chloride and that the two preparations have the o-tolyl radical attached to the ring-nitrogen, judging from the analyses. On hydrolysis both preparations give aniline and the o-tolyl-diketo compound, with no evidence of o-toluidine or of the phenyl-di-keto derivative. It was found that the di-keto compound may be obtained only from the acid mixture in the distilling flask, for this compound appears to break down in even a slightly alkaline solution when subjected to steam distillation, yielding thioacetic acid as one of the products.

The question arises in this connection as to what would be the results if this series of reactions were carried out with an alkyl and an aryl group

instead of with two aryl radicals. Such an investigation is planned.

Phenyl-ethyl amine, prepared by treating diethyl sulphate with aniline at 180 degrees, was treated with chloroacetyl chloride in the presence of pyridine and a little benzene. On pouring the mixture into water a heavy oil separates. This oil was digested in alcohol with KSCN. On dilution with water again a heavy oil separates. A nitrogen determination gave results corresponding to the formula, $C_{11}H_{12}ON_2S$, but whether the compound is the thiohydantoin or the thiocyano-derivative has not been determined. The product, however, has the physical appearance and consistency of the α,α-phenyl-ethyl thiohydantoin prepared from the sodium salt of phenyl thiohydantoin and ethyl iodide. Possibly the reactions indicated have taken place:

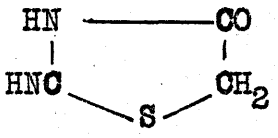




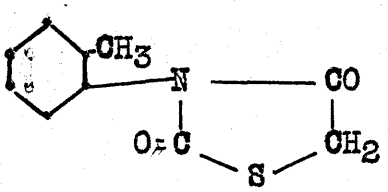
Chloroacet-o-toluidide and thiourea were digested in alcohol with the view of finding out what would happen. Paul J. Meyer (Ber. X, p. 1965) found that chloroacetanilide and thiourea when treated in this manner gave two products, one, the unsubstituted thiohydantoin, the

other the mono-substituted product.

The solution on standing over night deposited a few grams of a product whose melting point, 220 degrees, corresponds to that of the unsubstituted product:

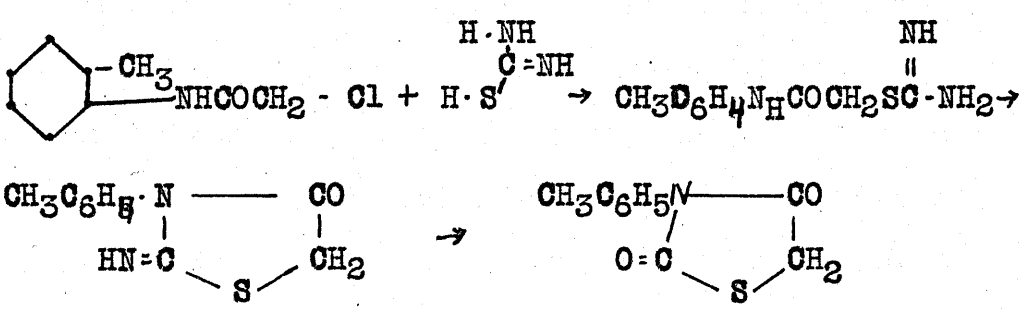


Evaporation of a large portion of the alcohol yielded no more of thispproduct. The concentrated solution diluted with water deposited some solid material whose analysis corresponds to the following structure:

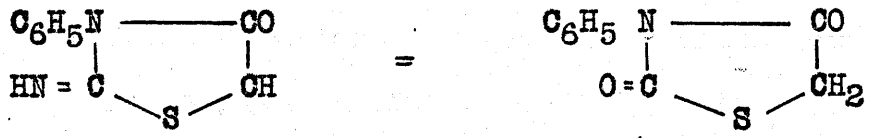


Nitrogen, Found, 6.48 Calculated, 6.76

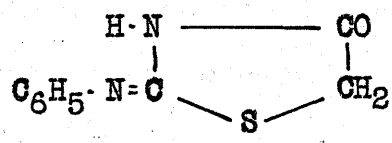
The filtrate from this product was found to be acid to litmus. On evaporation nearly to dryness the residue gives a positive test for ammonia on making alkaline. It also gives a positive carbylamine reaction. The product isolated would suggest the following reactions:



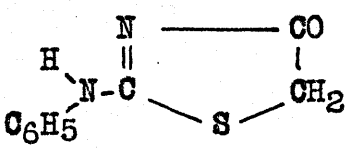
As has been stated before, Meyer obtained from phenylthiohydantoin, by boiling it with hydrochloric acid, 2, 4-diketo-3-phenyl-thiohydantoin:



Dixon, working with the same product, decided from the effect of carbon bisulphide upon it, that it has the constitution indicated by the formula,



Further, Wheeler and Johnson favor the idea of the existance of both forms, the latter being the more stable of the two. They also suggest the possibility of a third form, namely,



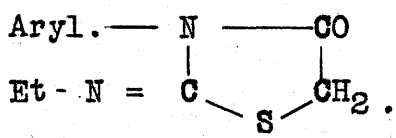
but discard it because the formula does not represent an alkali-soluble substance.

It would seem not inconsistant to consider the existance of all three forms in equilibrium with each other and that the apparent inconsistencies in results obtained by different investigators may be explainable on the assumption that the conditions of experiment determine which form predominates in any given reaction. The writer, in order to satisfy himself to some extent in this regard, tried the effect of 25 percent aqueous hydrochloric acid and of strong hydrochloric acid in alcohol, to determine whether these reagents differ any in their effects, first, upon a monosubstituted, second, upon a disubstituted thiohydantoin. He used for this purpose, o-tolylthiohydantoin and

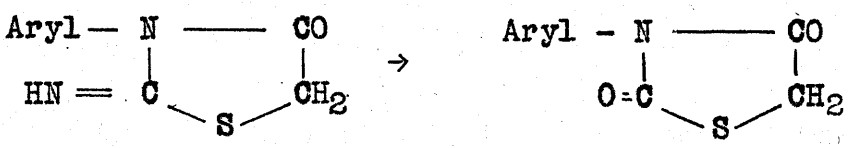
diphenylthiohydantoin prepared by methods which are supposed to give the 2-derivative for the former, and the 2, 3-compound for the latter.

It was found that both reagents had the same effect, the 2, -4-diketo-3-o-tolyl compound resulting in one case and the corresponding di-keto-phenyl product in the other.

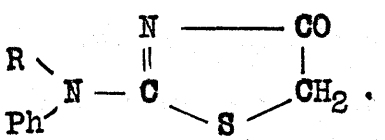
As has been mentioned before, Beckurts and Frerichs have assigned to their aryl-ethyl thiohydantoins the structure,



Apparently they assume this structure on the basis of the fact that they obtain, from some of their mono-aryl-substituted thiohydantoins, aryl mustard oil glycolides:

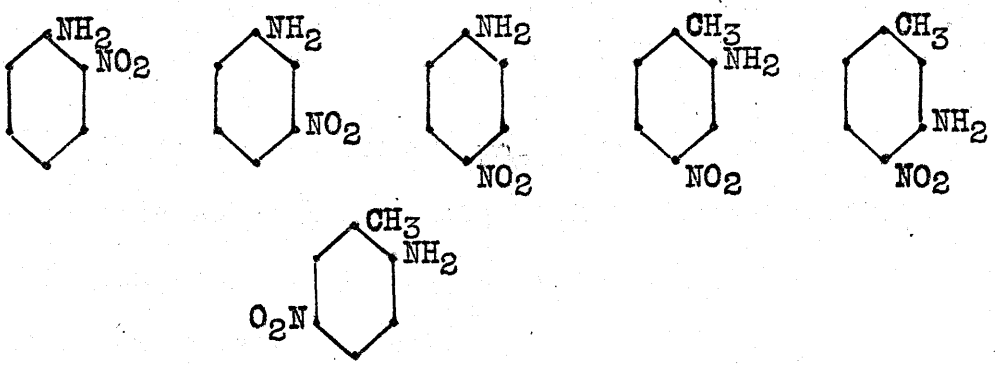


That this assumption may be erroneous has been shown by some work of Dains and Holmberg. These workers prepared a number of disubstituted thiohydantoins from the sodium salts of monoarylthiohydantoins and alkylhalides (and arylsubstituted-alkylhalides). These disubstituted compounds, on hydrolysis, they found to yield secondary amines, and, in some cases, dioxythiazole derivatives were obtained , facts which point to a union of the two substituting groups with the imino-nitrogen;



To test this point further some of the work of Beckurts and Frerichs was now repeated. The following six nitro-arylamines, which were among the primary amines used by these authors, were selected for the investigation:

Orthonitroaniline, Metanitroaniline, Paranitroaniline, Ortho-amino-para-nitrotoluene, Meta-amino-para-nitrotoluene, and Methyl-2-Amino-5-nitrobenzene.



These amines were converted into the respective chloracetarylamides by treating them with chloracetyl-chloride.

$$\text{Aryl-N}\begin{matrix}\text{H}\\\text{H}\end{matrix} + \text{Cl CO CH}_2\text{ Cl} \rightarrow \text{Aryl-NH·CO·CH}_3\text{·Cl} + \text{H·Cl}$$

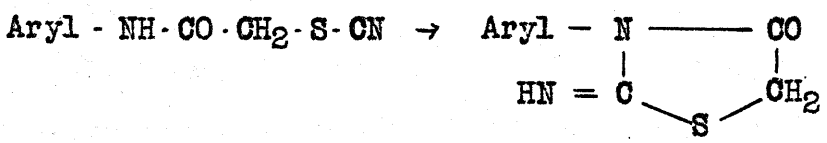
Be treating these compounds with potassium thiocyanate the corresponding thiocyanacetarylamides were obtained.

$$\text{Aryl·N H·CO·CH}_2\text{ - Cl + KCN} \rightarrow \text{Aryl - NH CO·CH}_2\text{·S·CN.}$$

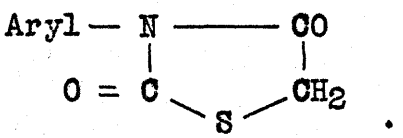
Beckurts and Frerichs (C. A. 10, 889-890) claim that the isothiodyanacetarylamide is first formed in certain cases but passes over into the normal compound.

By digesting these amides in boiling water for a long period,or in glacial acetic acid for a shorter period, the ring is closed and the aryl-substituted

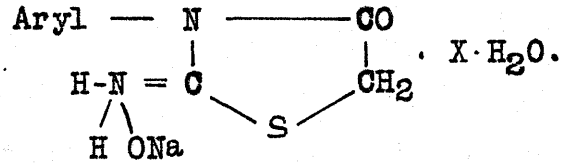
thiohydantoins were obtained.



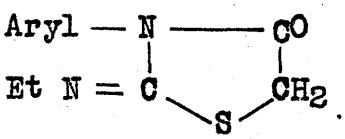
The structure given is that assigned by Beckurts and Frerichs and earlier by Meyer and others. The claim for this form is based upon the conversion of these products, on hydrolysis, into aryl derivatives of mustard oil glycolides:



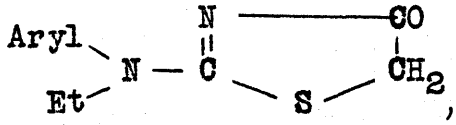
These thiohydantoins were converted into the sodium hydroxide salts by warming with a dilute solution of this reagent. These salts crystallize with a number of moles of water,



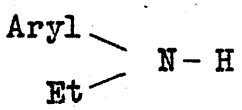
The salts with ethyl iodide gave the ethyl-aryl-disubstituted thiohydantoins to which Beckurts and Frerichs assigned the formula,



but for which our work seems to justify the structure;

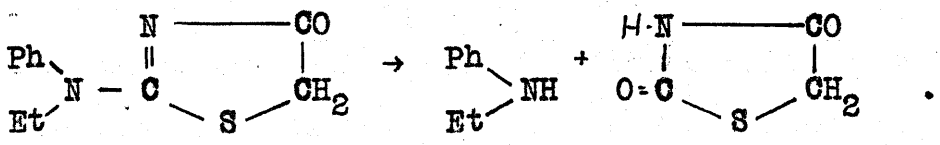


in virtue of the fact that, on hydrolysis, they yield secondary amines,

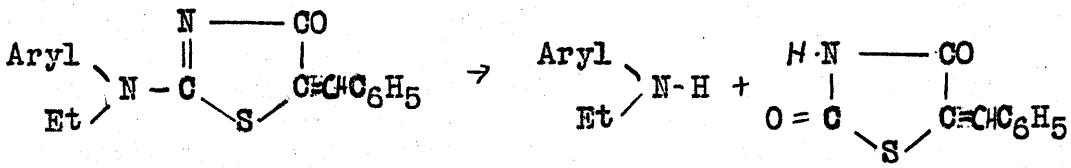


some of which, it was later learned, had been made and described.

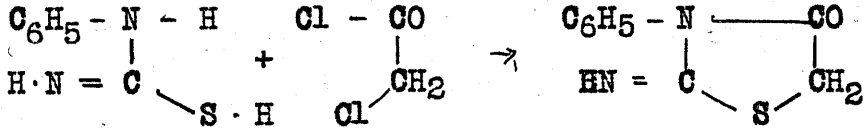
The phenyl-ethyl derivative was prepared. On hydrolysis it gave phenyl-ethyl amine and the unsubstituted mustard oil glycolide,



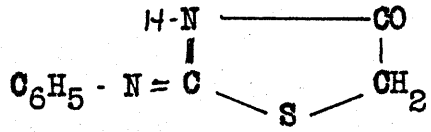
The benzal derivative of an aryl-ethyl substituted thiohydantoin gave, on hydrolysis, the secondary amine and the benzal-mustard-oil glycolide:



With the view of ascertaining what hydrolytic products might be obtained from a disubstituted thiohydantoin prepared by a different route, monophenylthiourea was treated with chloracetyl chloride on the assumption that they would react as follows:



giving the "labile" form of Wheeler and Johnson. The product was refluxed for a period with the view of converting it into the stable form:



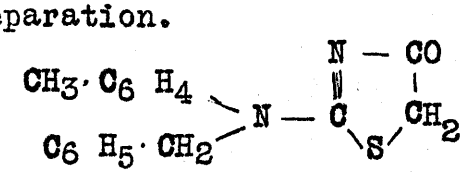
A yellow solid is obtained which with dilute sodium hydroxide yields shining flakes of the salt.

The salt with ethyliodide yields a dark-colored oil, which boils at about 250° C. The yield was too small to warrant an attempt to hydrolyze, and the experiment has not , as yet, been repeated.

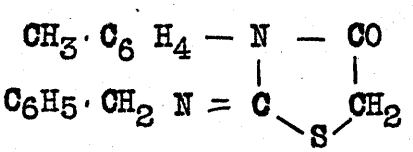
Thiourea and chloracet-benzylamide form an oily mixture which gradually solidified on standing at room temperature for more than a year. The solid melted at 220° and doubtless was the unsubstituted thiohydantoin. The experiment was one designed to determine whether the lower temperature would have any effect on the reaction.

Diphenyl thiohydantoin, on hydrolysis, gave aniline and phenyl-mustard-oil glycolide. The experiment was performed with the view of possibly obtaining some of the secondary amine which , if formed, would point to isomerization.

θ-tolyl-benzyl thiohydantoin prepared by the route of Beckurts and Frerichs, on hydrolysis, yielded the secondary amine, but in addition, a product is isolated whose nitrogen content corresponds to that of either o-tolyl- or benzyl-mustard oil glycolide. These results, in the light of subsequent work, point to the presence of isomerides in the disubstituted thiohydaantoin preparation.



and



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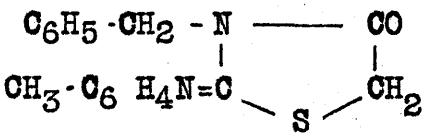


As has been previously stated, each of the disubstituted thiohydantoins, obtained by starting with the nitro-arylamines, on hydrolysis, gave a secondary amine, indicating these compounds to be of the α,α-type, and showing that the assumption of Beckurts and Frerichs was not well founded. While this proof was our primary objective, another very interesting fact developed in connection with this work and towards its close, namely, the recognition of isomers to which reference has already been made.

Previous workers, apparently, have not observed their presence. Dains and Holmberg however, found, on hydrolysis of their supposedly p-anisidin-ethyl- and -p-anisidine-benzyl-thiazolidones, some p-anisidine only. This fact suggests at least the possibility of the presence of isomerides in their preparations.

E X P E R I M E N T A L : P R E L I M I N A R Y

I. EXPERIMENTS WITH BENZYLAMINE.

1. CHLORACETBENZYLAMIDE, ($C_6H_5CH_2NH \cdot CO \cdot CH_2Cl$).

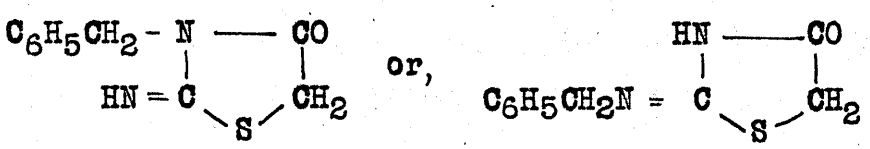
Chloracetyl Chloride, 11 grams.

Benzylamine, 16 grams.

Normal K O H sol. , 100 c. c.

The chloracetylchloride was added, drop by drop, to the mixed alkali and amine, with constant agitation and cooling of the mixture. A white solid immediately separated. Dissolved in alcohol and reprecipitated by addition of water, the product melted at 90-93°. A number of preparations by this method gave good yields of a pure white product. Results in a trial where pyridine was substituted for the alkali were not favorable.

2. BENZYLISOTHIOHYDANTOIN.



Molar quantities of chloracetbenzylamide and potassium thiocyanate were refluxed in alcohol for two or three hours. A white solid, which proved to be potassium chloride, separated. This was filtered off. On evaporating the alcohol from the

filtrate a red oil remained, which on dissolving in benzene and cooling, separated as crystals melting at 78-81°. The product is soluble in ether. Shaken out with dilute hydrochloric acid, the extract, on making alkaline, yielded a heavy white precipitate which melted sharply at 80°.

NITROGEN DETERMINATION.

Samples taken,	0.4150 gms.	0.3612 gms.
Standard acid,	25.00 c.c.	25.00 c.c.
Standard base,	16.40 c.c.	17.30 c.c.
Nitrogen equivalent,	8.60 c.c.	7.70 c.c.
Nitrogen obtained,	0.0587 gms.	0.0526 gms.
Nitrogen in control,	0.0031 "	0.0031 "
Nitrogen in Sample,	0.0556 "	0.0495 "
Percent nitrogen found,	13.399	13.704
Calculated for ($C_{10}H_{10}ON_2S$),	13.59	

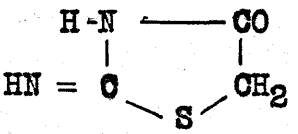
3. BENZYLISOTHIOHYDANTOINHYDROCHLORIDE.

($C_{10}H_{10}O\ N_2\ S$ - H Cl)

This was prepared by passing dry hydrogen chloride into a benzene solution of the isothiohydantoin. It was analyzed by titration with standard alkali.

Percent hydrogen-chloride, found,	14.80.
Calculated for ($C_{10}H_{10}ON_2S \cdot H\ Cl$),	14.93.

4. ISOTHIOHYDANTOIN and BENZYLCHLORIDE.



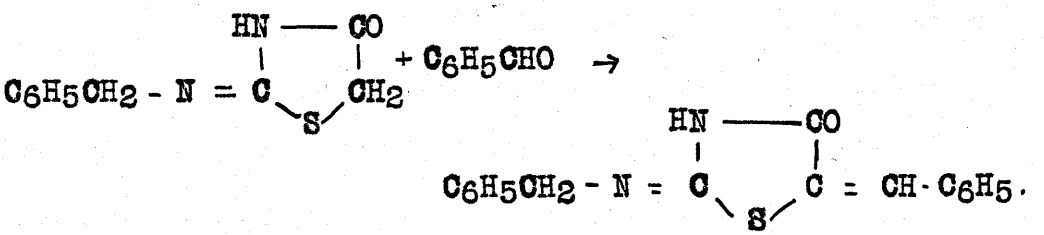
+ $C_6H_5CH_2 \cdot Cl$.

Molar quantities of these substances were treated with somewhat of an excess of a mole of aqueous potassium hydroxide. The mixture was allowed to stand, with occasional agitation, at room temperature, for several days. The solution was then subjected to distillation with steam to remove any remaining benzylchloride. On rendering the residue alkaline a heavy oil separated. A portion was dissolved in ether, the solution extracted with dilute hydrochloric acid, and the acid extract made alkaline. No solid separated, showing that the product was not the benzylisothiohydantoin previously described. The oil slowly solidified and melted at 54-57°. A nitrogen determination gave practically zero percentage. A qualitative test for nitrogen (sodium treatment and ferric-ferrous chloride) also gave negative results. Tests for sulphur (sodium treatment and nitroprusside test) gave positive results.

These results pointed to hydrolysis. The substance corresponds in melting point with benzylthioglycollic acid, and a portion dissolved in standard alkali and the excess of this reagent estimated by means of standard acid gave results

approximating the value calculated for this acid. Some of the filtrate obtained in the preparation on treatment with sodium nitrite and acid evolved nitrogen gas, indicating the presence of urea.

5. BENZYLTHIOHYDANTOIN and BENZALDEHYDE.

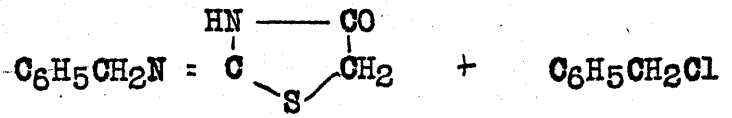


A mixture of these substances containing an excess of the aldehyde was heated for some time at a temperature of 180°. The resulting mixture on extraction with ether yielded a yellow powdery residue melting at 218°. It was found to be insoluble in water, alcohol and ether. After washing in boiling alcohol, an analysis of the product was made.

NITROGEN DETERMINATION.

Sample	0.4026 g.
Acid	42.26 cc N/5
Base	27.70 cc "
Control	0.41 cc "
Nitrogen, found, percent,	9.87
Calculated for ($C_{17}H_{14}ON_2S$)	9.53

6. BENZYLISOTHIOHYDANTOIN AND BENZYLCHLORIDE.



Molar quantities of these substances with somewhat over a mole of aqueous potassium hydroxide were digested for several days. On distilling with steam, making the residual solution acid, and extracting with benzene, a thick liquid was obtained which gave negative tests for nitrogen but positive tests for sulphur. The water-solution gave off a gas on treating with sodium nitrite. These results suggest, as in the case of isothiohydantoin and benzylchloride, that hydrolysis had taken place with breaking of the ring.

7. ISOTHIOHYDANTOIN and BENZYLCHLORIDE.

In previous attempts to prepare the substituted thiohydantoin from these substances, the excess of benzylchloride was removed by steam distillation. The possibility of hydrolysis being due to the high temperature suggested maintaining a low temperature throughout the experiment. In this test the temperature was not allowed to rise above that of the room. The excess of benzylchloride was removed by extraction with ether. The residual solution was then acidified. A heavy oil separated, as in previous cases, the product giving tests negative for nitrogen and positive for sulphur.

8. SILVER SALT OF ISOTHIOHYDANTOIN.

One equivalent of isothiohydantoin (1.45 g)

was dissolved in hot water, the solution cooled, and one equivalent of ammoniacal silver nitrate added from a burette. A heavy white precipitate formed, which settled slowly and was difficult to filter. Another trial in which the silver nitrate solution was added to the warm solution of the thiohydantoin resulted in a more granular precipitate. This was dried over calcium chloride in a vacuum dessicator and used in the following experiment.

9. SILVER SALT OF ISOTHIOHYDANTOIN and BENZYLCHLORIDE.

The silver salt (1.74 gms.) some benzene and an equivalent of benzylchloride were mixed and allowed to stand, with occasional shaking, for several days. At the end of this period, the mixture was filtered, the benzene removed on a water-bath and the liquid remaining distilled over a flame. The maximum temperature of distillation (173 Uncorr.) corresponds closely with that of benzylchloride (176°). The silver salt was recovered unchanged. Apparently these substances do not react under the conditions of the experiment.

10. CHLORACETBENZYLAMIDE and THIOUREA.

Molar quantities of these in alcohol were digested for three hours. A white solid separated. From hot water it melted at 220°. Evidently it was the unsubstituted isothiohydantoin. The distillate furnished ammonia and benzylamine.

The experiment repeated with the use of acetone instead of alcohol gave similar results as did also an experiment in which pyridine was used as a neutralizing agent.

Evidently in these experiments the primary reaction was in the direction of the formation of the unsubstituted thiohydantoin.

II. EXPERIMENTS WITH ETHYLAMINE.

1. CHLORACETETHYLAMIDE ($C_2H_5NH \cdot CO - CH_2Cl$).

One hundred grams of aqueous ethylamine (33%) were diluted with an equal volume of water, the solution cooled in a freezing mixture and 870 cc of 2-normal sodium hydroxide solution added. To this mixture 1.1 moles of chloracetylchloride (53.9 cc) were added drop by drop with vigorous shaking. At the end the solution was rendered slightly acid with acetic acid, and shaken out six times with ether. The ether solution was dried over calcium chloride, the ether removed by evaporation and the residue distilled in vacuo. Only about 7 grams of the amide were obtained.

2. CHLORACETETHYLAMIDE and POTASSIUM THIOCYANATE.

A mole each of the above were refluxed with alcohol. Potassium chloride separated and was

filtered off. The alcohol was removed by distillation, leaving a dark colored oil. An attempt to prepare the hydrochloride by passing dry hydrogen chloride into an ether solution of the product resulted only in the production of a brown sticky mass. Work with this yielded nothing definite at the time.

III. EXPERIMENTS WITH CHLORACETANILIDE.

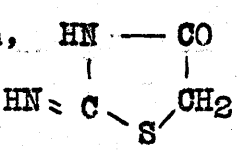
1. CHLORACETANILIDE. ($C_6H_5NH \cdot CO \cdot CH_2Cl$).

This product was prepared in quantity from chloracetyl chloride and aniline by gradual addition of the former to a cooled, well agitated benzene solution of the latter. On pouring the reaction mixture into a large volume of water the product separates as a nearly white crystalline solid.

2. CHLORACETANILIDE and THIOUREA.

These substances, (20 grams of the former and 10 grams of the latter) and acetone (60 cc) were refluxed for thirty minutes. Two layers of liquid formed in the flask, the lower one a brown oil. There was no evidence of evolution of HCl. The acetone was removed by distillation leaving a dark-colored oil, from which some crystals separate on standing and cooling. The semi solid was agitated with cold water. Some pale yellow crystals were

obtained which from hot water melted, but not sharply, in the neighborhood of 200°. This product was doubtless isothiohydantoin,



The filtrate from this solid, on evaporation, supplied a sticky residue. This when stirred with a little alcohol yielded a white solid, which, after thorough digestion with boiling water, melted at 176-177° (Uncorr.). This product was doubtless phenyl-isothiohydantoin (m.p. 178°).

The results of this experiment seem to show that the main reaction is towards the formation of the phenyl derivative, judging roughly from the relative amounts of the two products isolated. It should be noted that no neutralizing agent was employed.

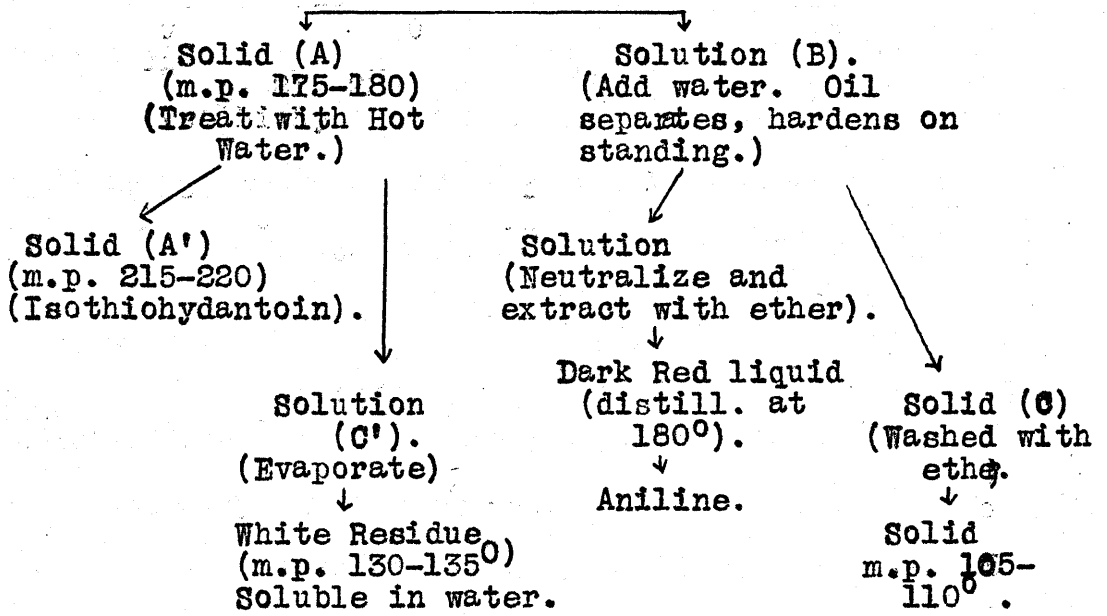
3. CHLORACETANILIDE, THIOUREA and PYRIDINE.

These materials in molar proportions were mixed and allowed to stand for 30 minutes and then refluxed for a similar period. On cooling and standing a few grams of solid melting at 217-221° had separated. The filtrate from this solid supplied aniline in considerable quantity. It seemed that in this experiment the main reaction was in the direction of the formation of the unsubstituted thiohydantoin.

In another similar attempt the results obtained are shown in the following diagram. It can be

seen from an inspection of this, that other products were present in addition to isothiohydantoin.

CHLORACETAMIDE & THIOUREA & PYRIDINE.



4. CHLORACETANILIDE and MONOPHENYLTHIOUREA.

(No Pyridine).

A mixture containing equivalents of the above substances was let stand for 15 hours at room temperature. No change took place from all appearances. The mixture was then refluxed for an hour and a half and allowed to cool, whereupon a mass of yellow crystals separated. The acetone was distilled off, leaving an apparently completely solid residue. This was digested with hot water, the mixture cooled and filtered. The yellow undissolved sodid, recrystallized from alcohol, melted at 176°. Mixed with pure diphenylthiohydantoin, it melted at about 145 degrees. The

product was therefore doubtless not the diphenyl- but the monophenyl thiohydantoin. The aqueous filtrate contained aniline.

This experiment was repeated with the exception that pyridine was used to take care of the acid formed during the reaction. In this case also, aniline was detected and a product isolated which corresponded in melting point with monophenyl-thiohydantoin.

5. CHLORACETANILIDE and SYMMETRICAL DIPHENYLTHIOUREA.

Molar quantities of these substances in acetone, were allowed to stand at room temperature for 20 hours and then digested on the water-bath for 45 minutes. On dilution with water, cooling and stirring a solid mass collects in a ball and white crystals remain suspended in the liquid. The filtrate reacted positive for aniline. The solid was dissolved in alcohol and reprecipitated by dilution with water. This precipitate began to melt at 120°. Mixed with diphenylthiourea it began melting at 125°. Boiled with alcohol a portion dissolves. On crystallizing out, it melted at 168-170°. (Mixed with diphenylthiohydantoin, 168-170°).

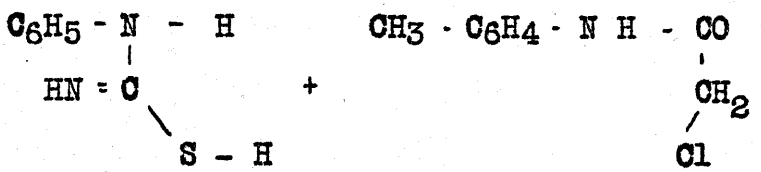
A repetition of this experiment in which pyridine was used as a neutralyzing agent gave similar results, the solid obtained melting at 120- degrees. Mixed with some of the 120° product

obtained above, it showed no change in melting point.

IV. EXPERIMENTS WITH CHLORACETTOLUIDE.

1. CHLORACETTOLUIDE and MONOPHENYLTHIOUREA.

In molecular proportions these were refluxed in acetone for a period of fifteen minutes. The acetone was distilled off and the residue treated with cold water. From the undissolved portion monophenylthiohydantoin was obtained (judged by the mixed melting point). From the filtrate toluidine was recovered.



2. CHLORACETTOLUIDE and DIPHENYLTHIOUREA.

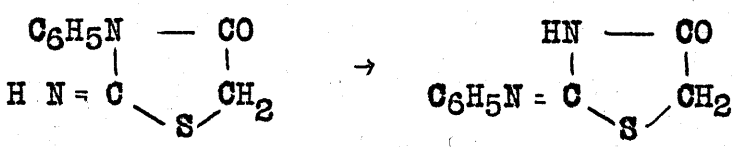
These were treated in a manner similar to (1) above. A solid was obtained which on treatment with alcohol yielded a crystalline substance melting at 156-158°. Mixed with diphenylthiohydantoin it melted at 159-161°.

V. EXPERIMENTS WITH ANILINE DERIVATIVES.

1. MONOPHENYLTHIOUREA and CHLORACETYLCHLORIDE.

Monophenylthiourea,	15 gms.
Chloracetylchloride,	11 gms.
Pyridine,	8 gms.

The chloracetylchloride was added slowly to the cooled mixture of the other substances. The resulting mixture was then poured into a large volume of water. A waxy, yellowish substance at first separated but slowly changed to a nearly colorless solid, yield, 12 gms. Refluxed in water it behaved in a manner similar to that of thiocyanacetanilide, which may mean that the 'labile' thiohydantoin of Wheeler and Johnson is the product first produced. From the hot water a yellowish cyrstalline substance is obtained.



2. PHENYLTHIOHYDANTOIN and SODIUM HYDROXIDE.

The thiohydantoin dissolved in warm 20 percent alkali and on cooling, flakes of the salt were deposited. Yield 2⅓ gms.

3. PHENYLISOTHIOHYDANTOIN! SODIUM HYDROXIDE and ETHYLDOIDE

These substances, in approximately molar

proportions were digested in alcohol for several hours. On steam distillation a heavy oil came over. The flask contents, on extraction with ether, yielded a dark-colored oil of boiling point approximately 250°. The extracted flask contents on rendering slightly alkaline and again steam distilled yielded some more of the oil. Doubtless in this case hydrolysis of an $\alpha\gamma$--disubstituted thiohydantoin occurred with the formation of phenyl-ethyl amine although this was not established as a fact at the time.

4. ANILINE and CHLORACETYLCHLORIDE.

Aniline, 18 gms.
Chloracetylchloride, 22 gms.

The latter compound was added slowly to a cooled benzene solution of the former. The reaction mixture was poured into a large volume of water whereupon a solid separated. From alcohol it gave colorless flakes melting at 130-131°. (Accepted for chloracetanilide, 134.5°). It was found that the use of pyridine apparently did not affect the yield which was always good.

5. CHLORACETANILIDE and POTASSIUM THIOCYANATE.

$C_6H_5NH \cdot CO \cdot CH_2 \cdot Cl$ $K \cdot S \cdot C \equiv N$

50 gms. 30 gms.

These substances were digested for an hour in alcoholic solution. The K·Cl was removed by

filtration and the bulk of the alcohol distilled off. On pouring the dark-colored liquid into water, an oil separates but changed gradually to a nearly colorless crystalline solid. A portion from hot water melted at 171-173°. Doubtless the product was mainly the thiohydantoin. Yield 40 gms.

6. THIOCYANACETANILIDE CONVERSION.

The whole yield from (5) was digested first with boiling water alone, and finally with water containing acetic acid. From the filtrate a yellow solid was obtained. The residue was a sticky black semisolid which melted on repeated digestion, but furnished very little more of the yellow solid. Melting point of the product from alcohol, 175° (Uncorr.). Accepted for phenyl-thiohydantoin, 178°. Yield 23 gms.

7. PHENYLTHIOHYDANTOIN and ALKALI.

The thiohydantoin was converted to the sodium hydroxide compound in the manner described in (3) above. Yield 22 gms.

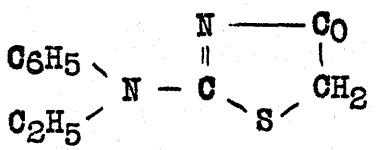
8. THE SODIUM SALT and ETHYL IODIDE.

The salt, 17 gms., and iodide, 14 gms., were digested in alcohol for eight hours. About half the alcohol was removed by distillation, leaving a dark-colored heavy oil. The final portion of the distillate contained no oil showing that

hydrolysis was not taking place during distillation, a condition which had been suspected in (3). Washed with water the oil had a chocolate color.

NITROGEN DETERMINATION.

Sample,	0.4018 gms.
Acid, N/5 ,	30.11 cc.
Base, " ,	11.49 cc.
Contol" ,	.41 cc.
Percent nitrogen, found,	12.69
Calculated for ($C_{11}H_{12}ON_2S$).	12.73



, ethylphenylthiohydantoin.

9. HYDROLYSIS OF ETHYLPHENYLTHIOHYDANTOIN.

This product was digested for eight hours with alcohol and strong hydrochloric acid. The alcohol was removed with steam. During distillation some oil was observed to come over. On rendering the solution barely alkaline with NaOH, an oil separated and rose to the surface. This was removed with steam, dried and subjected to analysis

NITROGEN DETERMINATION.

Samples,	0.4230 g.	0.2973 g.
Acid, N/5	30.11 cc.	22.08 cc.
Base, "	11.79 cc.	8.67 cc.
Control "	0.41 cc.	0.41 cc.

Percent N_2, found, 11.62 ~~12.84~~

Calculated for

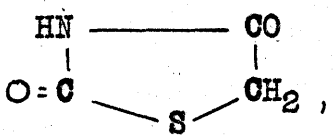
$C_6H_5 - NH - C_2H_5$, 11.57

10. SECOND PREPARATION OF α-PHENYLETHYLTHIOHYDANTOIN.

From 50 gms. of chloracetanilide there was obtained by the method previously described, 30 gms. of the -SCN derivative. The latter on digestion in water gave 20 gms. of the thiohydantoin This was digested with ethyl iodide in alcohol for a period of 16 hours. Half the alcohol was removed on the water-bath, the remainder, with steam. During steam distillation some light oil came over and had not ceased to come over after rather a long period. It occurred to the worker at the time that this oil might be a product of slow hydrolysis. It was noticed in this connection that the distillate was acid to litmus. In the distilling flask, on cooling, a thick dark oil settled out, from which was decanted the supernatent aqueous layer, (also acid to litmus). From this decanted layer, (along with a little of the heavy oil which came over), nearly colorless crystals separated. The oil also appeared to slowly take on a crystalline structure. The oil was repeatedly extracted with ether. From the ether extract a crystalline product separated. This softens at 116° and melts to a clear oil at 120°. Washed again in ether it melted at 119-121°.

The ether extract, on evaporation, left a dark-colored oil which showed no evidence of solidifying.

This behavior suggested that hydrolysis had occurred and that the solid obtained might be the mustard oil glycollide.



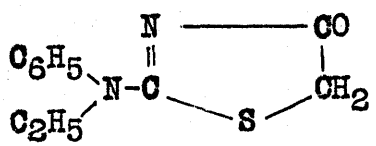
m.p. 121°.

NITROGEN DETERMINATION.

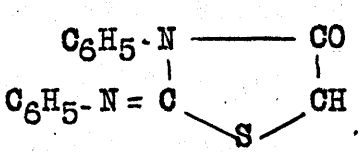
Sample,	0.4123 g.
Acid, N/5	30.11 cc.
Base, "	11.89 cc.
Control "	0.41 cc.
N_2 , found,	12.09 percent.
Calculated for ($C_3H_3O_2NS$)	11.97 percent.

This result suggests that the diketo compound may be obtained from substituted thiohydantoins provided hydrolysis takes place in a rather weak acid medium.

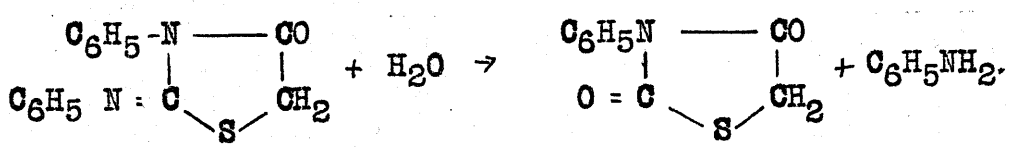
The outcome of (9) and (10) indicate the following structure for the phenyl-ethyl isothiohydantoin, obtained from the sodium salt and ethyliodide.



11. HYDROLYSIS OF α, β-DIPHENYLTHIOHYDANTOIN.



The above structure was assumed from the manner of formation of the product, namely, from symmetrical diphenylthiourea and chloracetic-ester. Digested in alcoholic hydrochloric acid for several hours a solid separated whose analysis is given below. From the filtrate aniline was isolated. This fact and the analytical results given below indicate the following reaction:



NITROGEN DETERMINATION.

Sample,	0.4015 g.
Acid, $^{N}/_{5}$	33.90 cc.
Base, "	23.00 cc.
Control,"	0.41 cc.
N_2, found,	7.31 percent
Calculated for ($C_9H_7O_2NS$),	7.26 percent.

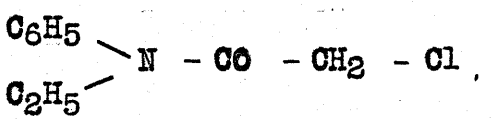
12. ANILINE and DIETHYLSULPHATE.

Aniline and an excess of the sulphate are heated at 150° for an hour. The resulting mixture is diluted with water, made alkaline with NaOH, and subjected to steam distillation. Ethylaniline comes over and floats on the surface of the aqueous distillate. Water is added to the receiving flask so as to bring the oil into the neck whence it is removed by means of a pipette.

$$2\ C_6H_5NH_2 + Et_2SO_4 = 2\ C_6H_5NH\cdot C_2H_5 + H_2SO_4.$$

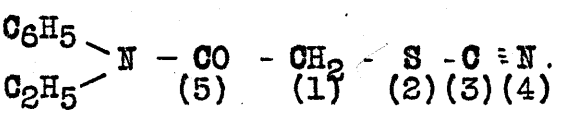
13. ETHYLANILINE AND CHLORACETYLCHLORIDE.

Chloracetylchloride, one mole, is added slowly to a cold solution containing a mole of ethylaniline in benzene. Diluted with water a heavy oil is obtained which presummably is chloracetphenylethylamide.

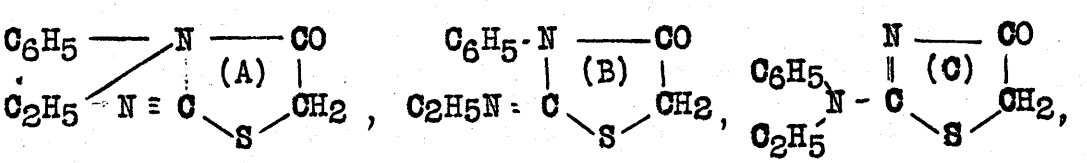


14. CHLORACETPHENYLETHYLAMIDE AND POTASSIUM THIOCYANATE.

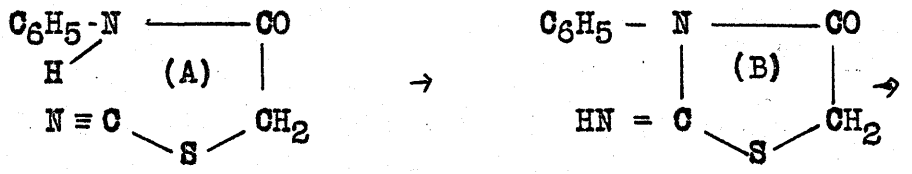
These substances in equivalent proportions are digested in alcohol for a half-hour. On filtering off the K·Cl and removal of alcohol by steam distillation a heavy dark-colored oil remains. This is taken to be thiocyanacet·phenyl·ethyl·amide.

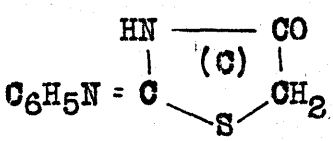


Whether this will rearrange to a thiohydantoin has not as yet been determined. A single nitrogen determination corresponds closely with the percentage calculated for the above compound (A). Rearrangement to the thiohydantoin would involve ring closure and a shift of the aryl or alkyl group, (B) or both, (C) to the imide nitrogen:

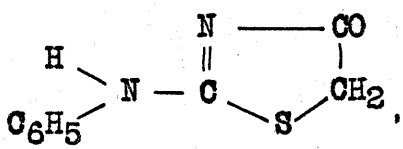


a process which does not seem to the writer to be inconsistent, inasmuch as a similar change is assumed in the case of thiocyanacetamide (A) with the initial formation of the 'labile' form (B) of Wheeler and Johnson and finally to the 'stable' form (C) of these workers:





, or possibly,



This point is being reserved for further investigation.

VI. EXPERIMENTS WITH o-TOLUIDINE DERIVATIVES.

1. O-TOLUIDINE AND CHLORACETYLCHLORIDE.

$CH_3 \cdot C_6H_4NH_2$	21 gms.
$Cl \cdot CH_2CL \cdot Cl$,	30 gms.
Pyridine,	15 gms.

The chloracetyl chloride is added slowly, as in other instances, to a cold mixture of the

other substances in a little benzene, or better, acetone, as solvent. Practically the calculated yield of the chloracetderivative is obtained on pouring the reaction mixture into water. From dilute alcohol long white needles are obtained, melting at 89-90°.

$CH_3 \cdot C_6H_4NH \cdot CO \cdot CH_2Cl$.

2. CHLORACET-o-TOLUIDE AND POTASSIUM THIOCYANATE.

$CH_3C_6H_4NH \cdot CO \cdot CH_2 \cdot Cl$,	80 gms.
$K \cdot S \cdot C : N$,	60 gms.
Alcohol,	300 cc.

This mixture was digested for 45 minutes, the K·Cl filtered off and washed with alcohol, and the filtrate and washings reduced in volume be distillation. A dark-red solution remains. When this is poured into water a dark-red oil separates, but solidifies on stirring to a more or less firm consistency. After standing for 48 hours a large proportion of the material had changed to a yellowish crystalline solid. The filtrate on further dilution yields more of the solid, which melts sharply at 173° .

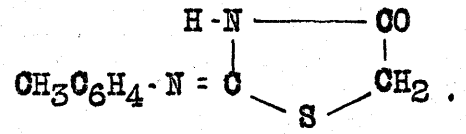
NITROGEN DETERMINATION.

Sample,	0.4443 g.
Acid, $N/5$	41,31 cc.
Base, "	19.45 cc.
Control,"	0.41 cc.

N_2, found, 13.52 percent.

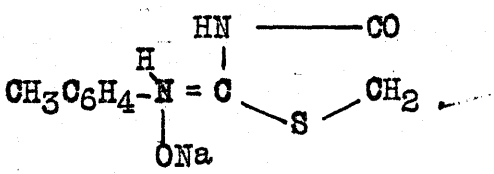
Calculated for ($C_{10}H_{10}ON_2S$)13.59 "

The product is doubtless the thiohydantoin, formed by rearrangement of the S CN-compound.



3. O-TOLYLISOTHIOHYDANTOIN AND SODIUM HYDROXIDE.

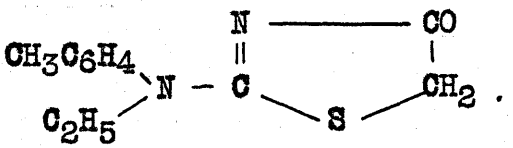
The sodium hydroxide-salt was formed as a crystalline solid by dissolving the thiohydantoin in warm 20% alkali and cooling,



4. THE SODIUM SALT AND ETHYL IODIDE.

Twelve grams of the salt and eight cubic centimeters of the iodide are digested for twelve hours in alcohol. Subjected to steam distillation, an oil separates on the top of the aqueous layer. The distillate continues cloudy and some clear oil rises to the surface in the receiving flask. Hydrogen sulphide is detected indicating that hydrolysis has ruptured the ring, and the distillate is alkaline to litmus. Distillation is continued until a liter of distillate has been collected. Cloudiness of the distillate continued to the end but the oil in the distilling flask had settled

to the bottom. The aqueous layer was decanted, the oil washed with water by decantation and subjected again to steam distillation. The distillate was still cloudy indicating, possibly, progressive hydrolysis. The oil remaining in the flask was assumed to be ethyl-o-tolyl-thiohydantoin:



NITROGEN DETERMINATION.

Sample,	0.3148 g.
Acid, N/5	40.15 cc.
Base, "	26. 30 cc.
Control, "	0.41 cc.
N_2, found,	11.95 percent.
Calculated for ($C_{12}H_{14}ON_2S$),	11.97 "

5. ATTEMPT TO HYDROLYZE o-TOLYL-ETHYLTHIOHYDANTOIN.

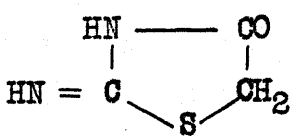
This product was digested in alcoholic H·Cl solution for several hours. Steam distillation of the acid reaction mixture yields a little light oil on surface of distillate. The contents of the distilling flask partially neutralized, but still, acid, on further steam distillation, gave no oil in the distillate. On rendering the mixture alkaline and steam distilling still no oil was obtained. The ferric chloride test for thioacetic acid on the flask contents was positive. Evidently hydrolysis

had taken place but other products escaped positive detection.

6. CHLORACET-o-TOLUIDE AND THIOUREA.

$CH_3C_6H_4NH \cdot CO \cdot CH_2Cl$,	20 gms.
$H_2N - C-S - NH_2$,	15 gms.
Alcohol,	250 cc.

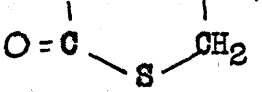
This mixture was digested for a time and then permitted to stand over night at room temperature. Some crystals had formed which on taking a melting point, start to change color at 150° and continue to change color up to 220°, when they are quite black. Some of the solid crystallizes white and then changes over a range of temperature from 200° to 223°. The product was doubtless isothiohydantoin (m.p. 220°)



, yield, about 4 gms.

The alcoholic solution was further digested and again allowed to stand but no further yield of the product was secured. The alcohol was then partially distilled off, and the residue cooled. A dark-red solution remains; no crystals. On addition of water a white precipitate formed. Heated to boiling, a solid separated which on drying possessed a very light chocolate color, and melting at 126-127°. The product was thought to be the

'labile' o-tolylthiohydantoin but further digestion failed to alter the melting point. The filtrate on evaporation to low bulk yielded a 'buttery' mass, acid to litmus and soluble in water. Some cloudiness developed on making this solution alkaline, ammonia was given off on warming, but tests for toluidine were negative. Analysis of the 126-127° product indicates it to be the diketo compound, hydrolysis doubtless having been due to the HCl formed, $CH_3C_6H_4 \cdot N$ ——— CO , in the reaction.



NITROGEN DETERMINATION.

Sample,	0.3667 g.
Acid, $^N/_5$	42.86 cc.
Base, "	33.96 cc.
Control, "	0.41 cc.
N_2, found,	6.48 percent.
Calculated for ($C_{10}H_9O_2NS$)	6.76 "

7. O-TOLYLTHIOHYDANTOINSODIUM HYDROXIDE AND BENZYLCHLORIDE.

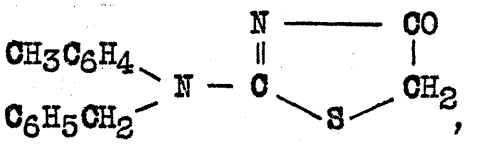
These substances, 15 grams of the former and 15 cc. of the latter, were digested in alcohol for nine hours. The salt, Na Cl, was removed by filtration and the filtrate subjected to steam distillation till the distillate ceased to come over cloudy. A dark-red oil, heavier than water, settled out in the distilling flask. Transferred to a beaker and cooled, the oil changed to a chocolate-

colored, sticky mass.

NITROGEN DETERMINATION.

Sample,	0.4712 g.
Acid, $^N/_5$	40.46 cc.
Base, "	25.14 cc.
Control, "	0.41 cc.
N_2, found,	8.86 percent.
Calculated for ($C_{17}H_{16}ON_2S$)	8.97 "

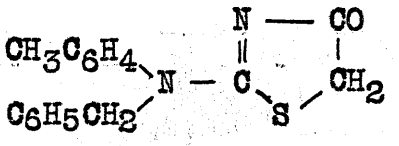
The product is pobably the disubstituted thiohydantoin:



an assumption to be confirmed by hydrolysis. An attempt to prepare the benzal derivative proved a failure.

8. HYDROLYSIS OF O-TOLYL-BENZYLTHIOHYDANTOIN.

The compound was subjected to hydrolysis in the manner described in former cases. The digestion mixture on distillation with steam yielded a 'non wolatile with steam' thick dark-colored semisolid, whose analysis corresponded with either o-tolyl, or benzyl-mustard-oil glycolide. An ether extract of the distillate gave the secondary amine, melting at 55°. Evidently here was a case of a mixture of at least two isomers.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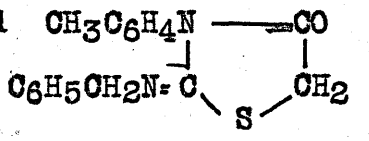
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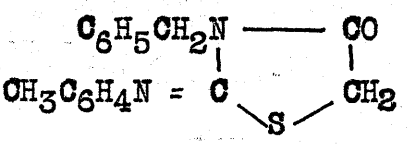
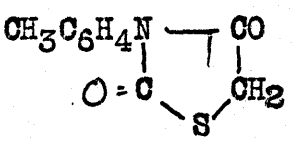


NITROGEN DETERMINATION.

A. On the Semisolid.

Sample,	0.3883	0.4763	
Acid, $^{N}/_{5}$	30.30	41.50	cc.
Base, "	21.00	29.20	cc.
Control "	0.41	6.99	percent

Calculated for,



$(C_{10}H_9O_2NS)$, 6.76 "

B. On The Secondary Amine.

Sample,	0.3972	
Acid, $^{N}/_{5}$	30.40	cc.
Base, "	19.30	"
Control, "	0.41	"
N_2, found,	7.54	percent

Calculated for

$(C_{14}H_{15}N)$,

$(CH_3C_6H_4 \cdot NH \cdot CH_2C_6H_5)$, 7.11 "

9. ETHYL-o-TOLUIDINE PREPARATION.

O-toluidine, 20 cc, and diethylsulphate, 20 cc,

were heated at 175° for 2⅓ hours. The mixture was then rendered alkaline and subjected to steam distillation. The amine comes over and floats on the surface of the distillate whence it is removed with a pipette. Yield 17.5 cc.

10. ETHYL-O-TOLUDDINE AND CHLORACETYLCHLORIDE.

Chloracetylchloride, 15 cc. were added to a cold solution containing 17 cc. of ethyl-o-toluidine and an equivalent of pyridine in acetone. Water was then added with stirring, when a heavy oil separated. This was washed with water and used in the preparation following.

$$CH_3C_6H_4\diagdown \atop C_2H_5\diagup N\text{-}H + Cl\cdot CO\cdot CH_2Cl = CH_3C_6H_4\diagdown \atop C_2H_5\diagup N - CO\text{-}CH\text{-}Cl.$$

11. CHLORACETETHYL-O-TOLUIDE AND POTASSIUM THIOCYANATE.

A mixture of these substances, containing 17 grams of the toluide and 15 grams of the cyanate, was digested in alcohol for 30 minutes. The K·Cl was filtered off and washed with alcohol. The filtrate and washings, on subjecting to steam distillation to remove the alcohol, supplies a red oil. Whether this is a thiohydantoin or the S C N - derivative has not, as yet, been determined. It is a preposition analogous to that of (V. 14) previously described and commented upon.

NITROGEN DETERMINATION.

Sample	0.4160 g.
Acid, $^{N}/_{5}$	42.16 cc.
Base, "	24.99 cc.
Control, "	0.41 cc.
N_2, found,	11.28 percent.
Calculated for,	11.95 "

$$CH_3C_6H_4 \diagdown \atop C_2H_5 \diagup N - CO \cdot CH_2SCN.$$

12. HYDROLYSIS OF ABOVE PRODUCT.

Four grams of this substance was digested with 32 cc. of 25 percent H Cl for 2½ hours. A heavy dark-colored oil was present in the flask. The acid aqueous layer was decanted, made alkaline and distilled with steam. The light oil which came over was found to be the secondary amine.

The heavy residual oil was subjected to further digestion with alcohl and concentrated H·Cl, for several hours. On rednering alkaline and steam distilling none of the amine came over. The product was then dried and a nitrogen determination made upon it.

NITROGEN DETERMINATION.

A. ON THE AMINE.

Sample,	0.4097 g.
Acid, $^{N}/_{5}$	41.30 cc.
Base, "	25.20 cc.

Control, $^{N}/_{5}$ 0.41 cc.

N_2, found, 10.72 percent.

Calculated for

$CH_3C_6H_4 \cdot NH \cdot C_2H_5$, ($C_9H_{13}N$) 10.37 ".

B. ON THE RESIDUAL OIL.

Sample, 0.4429.g.

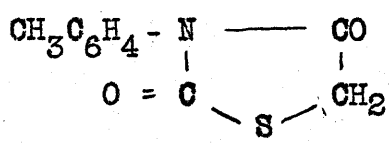
Acid, $^{N}/_{5}$ 42.70 cc.

Base, " 32.00 "

Control," 0.41 "

N_2, found, 16.51 percent

Calculated for



6.77 percent.

While the evidence presented is not sufficient to warrant the conclusion that ring closure has occurred, nevertheless the results are significant.

13. DI-o-TOLYLTHIOUREA.

O-toluidine	50 gms.
Carbon bisulphide	50 gms.
Alcohol (from lime)	50 gms.

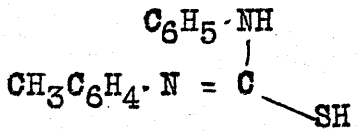
This mixture was digested for several hours. A solid separated. The alcohol and carbon bisulphide were removed by distillation and the residue washed with acidified water. Yield, dry 55 gms. Theory, 60 gms. From alcohol, m.p. 154°.

14. O-TOLYL-MUSTARD OIL.

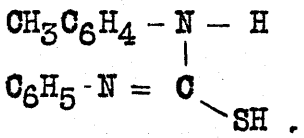
Di-o-tolylthiourea, 55 gms, was digested with concentrated H·Cl, 150 gms., for several hours. After two hours the solid began to show evidence of replacement with oil, and from then on the change was rapid. the product, a dark-colored oil, floating on the surface of the digestion mixture.
On distilling with steam the oil comes over in a practically colorless condition. It was removed with ether, dried and distilled. Boiling point, 231°. Yield 21 gms., or 69 percent of the theoretical amount.

15. O-TOLYLMUSTARD OIL AND ANILINE.

Ten grams of the former and 6.3 grams of the latter were warmed slightly. After a few minutes a firm, nearly colorless solid, had replaced the mixture of oils, the change taking place with the evolution of much heat. Melting point from alcohol, 134°. The product may be either one, or possibly a mixture, of the following substituted thioureas,

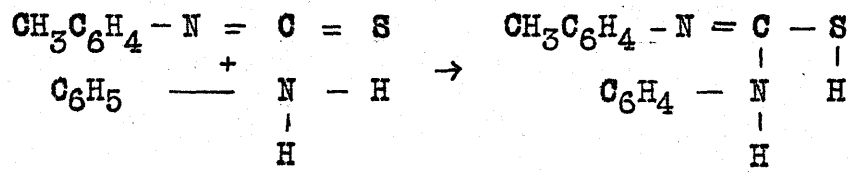


(A)



(B)

One would expect (A) if addition takes place as indicated below, and no shifting of radicles takes place,



16. O-TOLYL-PHENYLTHIOUREA AND CHLORACETYLCHLORIDE.

Five cubic centimeters of chloracetylchloride were added slowly to a cold solution containing 8 grams of the urea and somewhat less than an equivalent of pyridine in acetone. A white solid separated. The liquid was acid to litmus. Water was added whereupon a colorless oil, denser than water, separated but soon solidified. Melting point from dilute alcohol, 97°.

NITROGEN DETERMINATION.

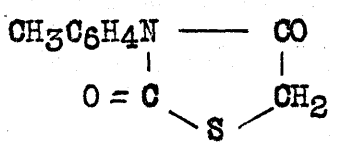
Sample,	0.37329
Acid, $^{N}/_{5}$	41.00 cc.
Base, "	27.30 cc.
Control,"	0.41 cc.
N_2, found,	9.94 percent,
Calculated for ($C_{16}H_{14}ON_2S$),	9.93 "

17. HYDROLYSIS OF O-TOLYL-PHENYLTHIOHYDANTOIN.

Ten grams of the thiohydantoin were digested with a solution containing 50 cc of alcohol and 25 cc. of concentrated H Cl for six hours. Some thick oil was found in the bottom of the flask after cooling. The acid mixture subjected to steam distillation yielded nothing. On cooling

again the oil showed a tendency to solidify. Some of the acid solution gave a negative test for thioacetic acid. The aqueous filtrate made alkaline and steam distilled, gave a good supply of aniline in the distillate. A test now for thioacetic acid was positive indicating clearage of the ring in the alkaline medium. Analysis of the solid product corresponded to that for o-tolylmustard oil glycolide.

NITROGEN DETERMINATION.

Sample,	0.4862 g.
Acid, $^{N}/_{5}$	30.40 cc.
Base, "	18.55 cc.
Control,"	0.41 cc.
N_2, found,	6.59 percent.
Calculated for	
	6.76 percent.

18. DIPHENYLTHIOUREA.

A supply of this compound was prepared from aniline and carbon bisulphide in the manner outlined for the preparation of di-o-tolylthiourea.

19. PHENYLMUSTARD OIL.

This was prepared from diphenylthiourea in the same way that o-tolylmustard oil was obtained from di-o-tolylthiourea.

20. PHENYLMUSTARD OIL AND o-TOLUIDINE.

Ten grams of the mustard oil and eight of the toluidine were mixed. Solidification began almost immediately with evolution of heat. From alcohol the product melted at 134°. Mixed with the product from (15) above the melting point remained unchanged, signifying the identity of the two preparations and hence a selective action on the part of the two aryl groups concerned.

21. PHENYL-o-TOLYLTHIOUREA AND CHLORACETYLCHLORIDE.

Ten grams of the urea and five cc. of the chloride and an equivalent of pyridine were used in this experiment. The method involved being the same as that used in (16) above. The reaction mixture on dilution with water supplies an oil which on agitation changes to a white solid.

NITROGEN DETERMINATION.

Sample,	0.4124 g.
Acid, $^{N}/_{5}$	40.70 cc.
Base, "	25.80 cc.
Control,"	0.41 cc.
N_2, found,	9.84 percent.
Calculated for ($C_{16}H_{14}ON_2S$),	9.93 "

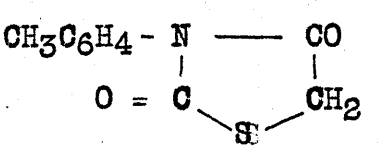
22. HYDROLYSIS OF PHENYL-o-TOLYLTHIOHYDANTOIN.

Ten grams of this product were digested with 50 cc. of alcohol and 25 cc. of concentrated

hydrochloric acid for 5½ hours. On cooling a dark-colored oil separated. The acid mixture subjected to steam distillation yielded nothing. On cooling, the aqueous portion was decanted and the thick oil washed with water. The acid filtrate showed a negative test for thioacetic acid but on rendering it alkaline and steam-distilling, aniline came over in quantity. A test for thioacetic acid on the resulting alkaline solution showed its presence, a fact which indicates rupture of the ring. The thick oil was digested further with alcohol and concentrated H-Cl for an hour and a half. On steam distilling the acid solution no oil came over. The aqueous portion was then made alkaline and again steam distilled. Some aniline came over as indicated by the hypochlorite test. The heavy oil was analyzed.

NITROGEN DETERMINATION.

Sample,	0.4646 g.
Acid, $^{N}/_{5}$	40.30 cc.
Base, "	29.10 cc.
Control,"	0.41 cc.
N_2, found,	6.51 percent.
Calculated for,	



, 6.76 "

E X P E R I M E N T A L : P R O P E R

I. EXPERIMENTS WITH O-NITROANILINE DERIVATIVES.

1. CHLORACET-O-NITROANILIDE.

O-nitroaniline	20 gms.
Chloracetylchloride	14 cc.
Pyridine	12 cc.

The chloracetylchloride was added slowly with stirring to a cold acetone solution of the nitroaniline and pyridine. On pouring into a large volume of water the anilide separated as a yellow solid. Melting point (Beckurts and Frerichs) 88°.

2. THIOCYANACET-P-NITROANILIDE.

Chloracet-o-nitroanilide	25 gms.
Potassium Thiocyanate	15 gms.

This mixture was digested in boiling alcohol for from fifteen to twenty minutes. On filtering off the potassium chloride the filtrate on dilution with water yielded a powder melting in the neighborhood of 160°. Evidently partial conversion to the thiohydantoin had taken place, inasmuch as

Beckurts and Frerichs report a melting point for the -S·C:N compound of 154° and also refer to its ease of conversion.

3. O-NITROPHENYLTHIOHYDANTOIN.

The thiocyano-derivative was digested with successive large volumns of water for long periods. A yellow solid decreasing in depth of color with the extraction melting at 170-171°. (Beckurts and Frerichs 172°).

4. O-NITROPHENYLTHIOHYDANTOIN SODIUM HYDROXIDE.

O-nitrophenylthiohydantoin, 7 grams, was treated with warm 20% Na OH solution and the yellow product which separated on cooling, filtered off and dried on a poreous plate. It is reported by Beckurts and Frerichs as containing three moles of water of crystallization.

5. ETHYL-O-NITROPHENYLTHIOHYDANTOIN.

Na OH - Compound,	10 gms.
Ethyl Iodide,	5 cc.
Alcohol,	75 cc.

The above mixture was digested for several hours. The alcohol and excess of ethyl iodide were removed with steam and the residue washed with water. A dark-brown syrup-like substance was obtained. It is described by Beckurts and Frerichs

as "a light brown, thickly flowing oil."

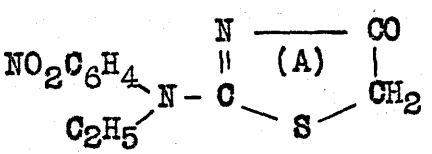
6. HYDROLYSIS OF ETHYL-o-NITROPHENYLTHIOHYDANTOIN.

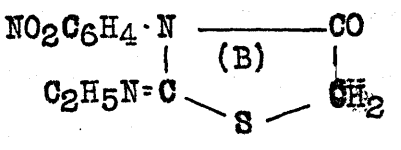
This product was digested with alcohol and strong hydrochloric acid for several hours. On distilling with steam a yellow distillate came over from the acid reaction mixture. The mixture was then rendered alkaline and distillation continued. A yellow oil then came over. This was taken up with ether, dried over $CaCl_2$ and recovered by driving off the solvent.

NITROGEN DETERMINATION.

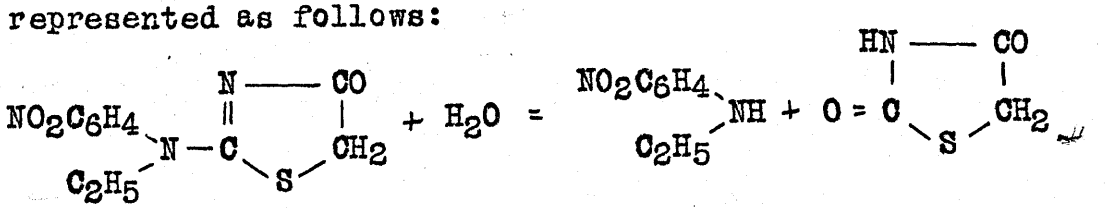
Sample,	0.4237 g.
Acid, $^{N}/_{5}$	40.15 cc.
Base, "	13.70 cc.
Control, "	0.41 cc.
N_2, found,	17.21 percent
Calculated for ($C_8H_{11}O_2N_2$)	16.87 "

This result points to the structure (A) for the thiohydantoin rather than the structure (B) assigned by Beckurts and Frerichs.





The reaction on hydrolysis would then be represented as follows:



NOTE: For the determination of nitrogen on the above compound and on succeeding nitro-compounds the following described method was used:

To the sample in the Kjeldahl flask, 30 cc. of concentrated $H_2 \cdot SO_4$ were added. After warming to dissolve the sample 2 grams of zinc-dust were added in small portions at a time, accompanied by shaking of the flask. After some further gentle heating of the contents, 10 grams of $K_2 SO_4$ and a drop (about .7 gms.) of mercury were added and the flask heated over a flame till the contents became colorless. On cooling sufficiently, 300 cc of water were added followed with 30 cc of potassium iodide solution (40 gms. per liter). After shaking thoroughly, 100 cc of Alkali (60 gms. per 100 cc of water) were run down the side of the neck of the flask, the latter then attached to a distillation apparatus, the contents of the flask mixed by shaking, and finally subjected to distillation into standard acid. In each case after a reasonable quantity of distillate had been collected, and the excess of acid titrated, a second period of distillation was resorted to with the view of assuring the complete removal of ammonia.

II. EXPERIMENTS WITH M-NITROANILINE DERIVATIVES.

1. CHLORACET-M-NITROANILIDE.

A number of preparations of this product were made of which the following may suffice for illustration:

M- nitroaniline,	14 gms.
Chloracetylchloride,	12 gms.
Pyridine,	16 gms.

As in other preparations of this nature, the chloracetylchloride was added slowly to a cooled mixture of the other substances with the addition of some benzene or acetone, preferably the latter. Godd yields of the product, described by Beckurts and Frerichs as small yellowish, almost white leaflets melting at 114° , were obtained.

2. THIOCYANACET-M-NITROANILIDE.

Chloracet-m-nitroanilide,	125 gms.
Potassium thiocyanate,	75 gms.
Alcohol,	350 cc.

This mixture was kept on a steam bath for an hour. A mass of crystals separated. A sample from alcohol melted at 200°, while a portion not recrystallized melted at 196-199°, (Beckurts and Frerichs, for the thiohydantoin, 199°). An attempt was made to recrystallize the whole product from alcohol. Digestion with alcohol appeared to alter the product, a dark-colored solution resulting

which deposited a black material. Dilution of the alcoholic solution with water yielded very little. The residue not dissolved by alcohol melted at 200°. This was used in the preparation of the Na OH, -salt, since it was evidently the thiohydantoin described by Beckurts and Frerichs.

3. SODIUM HYDROXIDE COMPOUND.

Forty grams of the thiohydantoin were warmed with 20% Na OH solution to the initial appearance of a blood-red solution. A yield of the salt of 50 grams was secured.

4. M-NITROPHENYL-ETHYL-THIOHYDANTOIN.

Fifty grams of the salt and 20 cc of ethyl iodide were heated in alcohol for several hours. On filtering and steam distilling a thick, sticky black oil remained in the flask. This was washed by decantation withhot water. It is described by Beckurts and Frerichs as 'similar to the o-derivative.' A low yield of the product may be due to insufficient digestion of the original substances.

5. HYDROLYSIS OF M-NITROPHENYLETHYLTHIOHYDANTOIN.

To the oil in the distilling flask 100 cc of alcohol and 30 cc of concentrated H Cl were added, and the mixture digested for several hours. The

alcohol was removed with steam, the residue made alkaline with Na OH and again steam-distilled. Seven grams of a yellow product came over, melting at 53-54°.

NITROGEN DETERMINATION.

Sample,	0.4367 g.
Acid, $^{N}/_{5}$	45.17 cc.
Base, "	18.17 cc.
Control,"	0.41 cc.
N_2, found,	16.62 percent
Calculated for ($C_8H_{10}O_2N_2$)	16.87 "

6. PREPARATION OF M-NITROPHENYLETHYL AMINE.

Metanitroaniline was heated in alcohol with an excess of diethylsulphate for an hour or more. Poured into an alkaline solution and the resulting mixture subjected to steam distillation an oil comes over which on cooling solidifies as orange colored crystals, melting at 52-53°. A mixture with the product of hydrolysis from (5) the melting point remains unchanged, thus showing the identity of the two products.

7. M-NITROPHENYL-ETHYL-5-BENZALTHIOHYDANTOIN.

This product was made by dissolving m-nitrophenylethylthiohydantoin in alcohol, adding an excess of benzaldehyde and a little Na OH solution, warming and allowing to stand at room

temperature. A solid separated in a short time. This was filtered off, digested in ether, in which it is insoluble, dried and analyzed.

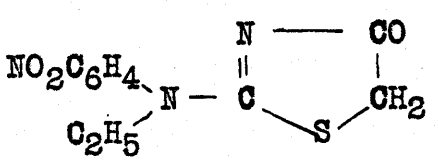
NITROGEN DETERMINATION.

Sample,	0.3396 g.
Acid, $^{N}/_{5}$	42.16 cc.
Base, "	26.70 cc.
Control,"	0.41 cc.
N_2, found,	12.41 percent.
Calculated for ($C_{17}H_{15}O_3N_3S$)	12.32 percent.

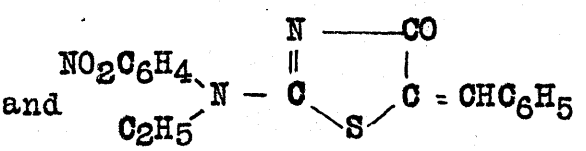
8. HYDROLYSIS OF THE BENZAL COMPOUND.

The benzal-product was heated for a long period with alcohol and concentrated H Cl-solution. A solid separates which was removed by filtration and found to melt at 170+°. The filtrate, made alkaline and steam-distilled gave the secondary amine obtained in (5) and (6).

The above results indicate the following structure for the thiohydantoins described:



and



III. EXPERIMENTS WITH P-NITROANILINE.

1. CHLORACET-P-NITROANILIDE.

The method of preparing this compound in no way differed from that of the two previous cases. The product described by Beckurts and Frerichs as melting at 182° was obtained in good yields.

2. THIOCYANACET-P-NITROANILIDE.

Chloracet-p-nitroanilide,	20 gms.
Potassium thiocyanate,	20 gms.

A mixture of these substances in alcohol was digested for an hour and a half. Other preparations were made with better results where the time of digestion was reduced to 30 minutes. On filtering and diluting the filtrate with water, the product described by Beckurts and Frerichs as melting at 174° was obtained in good yields.

3. P-NITROPHENYLTHIOHYDANTOIN.

The S·C:N - derivative was digested in boiling water for several hours, and the solution filtered hot. The filtrate deposited bright-yellow crystals melting above 200° . The product was taken as the thiohydantoin of Beckurts and Frerichs melting at 245°.

4. THE SODIUM HYDROXIDE COMPOUND.

This was prepared from the thiohydantoin by treating the latter with enough 10% NaOH solution

to make a thick paste. This was warmed on the water-bath and then cooled in ice-water. Experience had shown in dealing with the meta-compound that heating with alkali probably decomposed the product, inasmuch as the salt could not be obtained except in small quantities, the blood-red filtrate refusing to yield the latter even on treating with brine. It had also been observed that the filtrate on making acid with acetic acid failed to yield the original product. According to Beckurts and Frerichs the salt crystallizes with four moles of water.

Later preparations of this and other sodium hydroxide compounds gave more satisfactory yields by the use of an equivalent of 5% alkali, heating the mixture till solution took place and then cooling.

5. P-NITROPHENYL-ETHYLTHIOHYDANTOIN.

Note: The work in connection with this compound was attended with a great deal of perplexity and a number of preparations had to be made before satisfaction on the part of the worker was secured.

p-nitrophenyl-thiohydantoin,	10 gms.
Ethyl iodide	6 cc.
Alcohol,	60 cc.

This mixture was digested for five hours. (Later preparations showed that longer periods of digestion gave better yields). On distilling with steam, a dark-colored semisolid was left in the

distilling flask. Dissolved in alcohol and the solution poured on ice, a light-yellow colloidal suspension resulted, which, on standing, deposited a yellow solid. From hot water, it melted at 125+°. Hydrolysis of this preparation, ~~was~~ were refluxed with 25 cc. of 25% H Cl-solution for 17 hours. is here described. Three grams of the product

On neutralizing a portion of the reaction-mixture with soda-ash and steam-distilling, a yellow distillate is obtained. Such a distillate is also obtained by steam-distilling p-nitroaniline. The remaining portion of the acid reaction-mixture, on cooling, deposits yellow crystals melting at 145-146°. Mixed with some p-nitroaniline it melts at 145-147°, thus showing their identity.

This result was confusing, but was rendered clear in the light of later experiments.

Still another preparation of ethyl-p-nitro-phenylthiohydantoin, in which 12 hours were employed for digestion, was made. Ten grams of the sodium salt and 4 cc. of ethyl iodide were used. The digestion mixture formed a mass of crystals on cooling and shaking. After steam-distillation, an oil separated, which, from alcohol, afforded brown crystals melting at 130-131°. (Beckurts and Frerichs, 129°.)

NITROGEN DETERMINATION.

Sample, 0.3156 g.

Acid, $^{N}/_{5}$	28.94 cc.
Base, "	10.80 cc.
Control,"	0.55 cc.
N_2, found,	15.62 percent.
Calculated for ($C_{11}H_{11}O_3N_3S$)	15.85 percent.

HYDROLYSIS OF ABOVE PRODUCT.

Four grams of the product, 50 cc. of 25% H Cl solution and a little alcohol were digested for 14 hours. Ammonia was added short of neutralization when a yellow solid separated. The product was removed with ether, dried and analyzed.

NITROGEN DETERMINATION.

Sample,	0.3187 g.
Acid, $^{N}/_{5}$	30.35 cc.
Base, "	10.55 cc.
Control,"	.055 cc.
N_2, found,	17.07 percent,
Calculated for ($C_8H_{10}O_2N_2$)	16.87 "

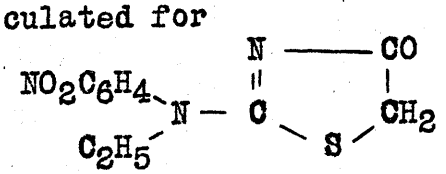
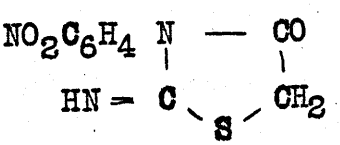
Another preparation of the thiohydantoin in which digestion was continued for a longer period, gave more of the product, which, from strong alcohol, melted at 126-127°. This was considered to be the product of Beckurts and Frerichs melting at 129°.

A new supply of the sodium salt was then prepared as follows: 35 grams of the thiohydantoin were mixed with an equivalent of 5% sodium hydroxide.

A thick mass of crystals resulted, from which the liquid (blood-red in color) was removed by suction. The product, dried carefully, to avoid decomposition, on the hot-plate, is a brown powder.

10 grams of this powder, 3 cc of ethyl iodide, and 15½ cc of alcohol (from lime), were sealed in a tube and heated in steam for an hour. The reaction mixture was steam-distilled, when a heavy black oil separated out in the distilling flask. From the aqueous layer, on cooling, a yellow, flocculent solid, separated. The oil became semi-solid in ice-water, and formed a black lump weighing 10 grams. An alcoholic solution, diluted with water slowly deposited a greenish-yellow solid. Analysis of this product, however, did not agree with that expected for the ethyl derivative.

NITROGEN DETERMINATION.

Sample,	0.3310 gms.
Acid, $^{N}/_{5}$	30.05 cc.
Base, "	8.72 cc.
New control, $^{N}/_{5}$	.55 cc.
N_2, found	17.58 %
Calculated for 	15.85 %
Calculated for 	17.72 %

The product obtained in this case evidently was not the ethyl-p-nitrophenyl thiohydantoin. It may have been the mono-aryl derivative. If so, its presence could be accounted for on the assumption that some of it escaped neutralization on treatment with alkali.

Another preparation afforded the analytical results outlined below.

NITROGEN DETERMINATION.

Sample,	0.3019 gms.
Acid, $^{N}/_{5}$	26.50 cc.
Base, "	10.10 cc.
Control,"	0.55 cc.
N_2, found,	14.87 %
Calculated for, ($C_{11}H_{11}O_3N_3S$)	15.85 %

Evidently not the product expected, or contains impurities.

The sample was dried further at a temperature of 200°.

NITROGEN DETERMINATION ON THE HEATED PRODUCT.

Sample,	0.3250 g.
Acid, $^{N}/_{5}$	30.16 cc.
Base, "	11.19 cc.
Control,"	0.55 cc.
N_2, found,	15.87 %
Calculated for ($C_{11}H_{11}O_3N_3S$),	15.85 %

Various attempts to hydrolyze this product

yielding negative or perplexing results, it was not until over a year later, that, returning to this subject, the experiments which follow lead to a clearing up of the problem, the solution of which had been suggested by the recognition and identification of isomerides in connection with the work with derivatives of o-nitro-p-toluidine.

The whole series of reactions starting with p-nitroaniline was repeated, with great attention to details. The preparations up to that of the ethyl derivative ~~compound~~ need no further description. The preparation of the ethyl-derivative, however, will bear further description.

6. P-NITROPHENYL-ETHYLTHIOHYDANTOIN.

The sodium salt,	20 gms.
Ethyl iodide,	8 cc.
Alcohol, (95%),	60 cc.

This mixture was refluxed for 14½ hours. On cooling in ice-water there was very little evidence of crystal-formation, until an attempt to filter was made, when quite a large mass of crystals formed on the filter and in the filtrate. The residue on the filter-paper was washed with hot alcohol.

This solution, on cooling, deposited a mush of silk-like crystals (A). Melting point 131-132°. The color of these crystals were not yellow as described by Beckurts and Frerichs but were flax-

like in color, or a dirty-white. Besides, their product melted at 129°, a fact, however, when considered alone does not signify a great deal.

The diluted filtrate, however, gave a yellow crystalline solid (B) melting at 127°. This with some of a previous preparation melting at 126-127° (see paragraph (5)) showed a mixed melting point of 127-129°, but with some of (A) melted at 105-110°, thus indicating that these two products were not the same compound.
The alcoholic solution from which the (A) had been filtered, on steam distillation, left an oil in the flask, which on cooling stiffens up to a mass having the color and consistency of chocolate. A yellowish solid, however, gradually separated from it melting at 127-129°. With (A) it melted at 105-110°.

IT IS TO BE NOTED HERE THAT (A) HAD CRYSTALLIZED FROM HOT STRONG ALCOHOL WHILE (B) WAS READILY SOLUBLE IN COLD ALCOHOL.

A portion of the chocolate-colored product however, continued semi-solid. Washed with ether it leaves undissolved, a brown residue melting at 127-128°. Mixed melting point with (B) unchanged (127-129°) . (Probably the same product although differing much in physical appearance).

The ether extract, on evaporation, yields a yellowish solid melting at 103-110°. Washed with

ether there is left a residue (C) melting at 104-105°. Washed further with ether, the product melts sharply at 103.5°.

Evidently the three products (A), (B), and (C) are not identical. Analyses of these follow:

7. NITROGEN DETERMINATION ON PRODUCT (A).

Sample,	0.2235 g.
Acid, N/5	24.40 cc.
Base, "	13.18 cc.
New Control, N/5	0.50 cc.
N_2, found,	15.88 %
Calculated for ($C_{11}H_{11}O_3N_3S$)	15.85 %

8. NITROGEN DETERMINATION ON PRODUCT (B).

Sample,	0.2134 g.
Acid, N/5	23.05 cc.
Base, "	10.50 cc.
Control,"	0.50 cc.
N_2, found,	15.81 %
Calculated for ($C_{11}H_{11}O_3N_3S$)	15.85 %

9.. NITROGEN DETERMINATION ON PRODUCT (C).

Sample,	0.1395 g.
Acid, N/5	24.60 cc.
Base, "	16.32 cc.
Control, "	0.50 cc.
N_2, found,	15.78 %
Calculated for ($C_{11}H_{11}O_3N_3S$)	15.85 %

Evidently (A), (B), and (C) are isomeric substances.

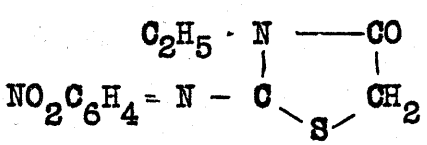
10. HYDROLYSIS OF ISOMER (A).

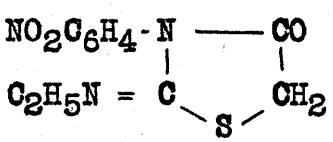
Three grams of (A), 20 cc of alcohol and 25 cc of concentrated HCl solution were heated at boiling temperature for 18 hours. There was no solid to filter off. Diluted with water, a cloudiness developed, but no solid separated. Made alkaline with soda-ash a greenish-yellow precipitate formed.

Melting point of this product,	146° sharp.
Mixed with p-NO_2 aniline,	146-148°
Yield of product,	0.835 gms.
Percentage yield,	53.5

Conclusion:

(A) may be represented by one or the other of the following structures,





11. HYDROLYSIS OF ISOMER (B).

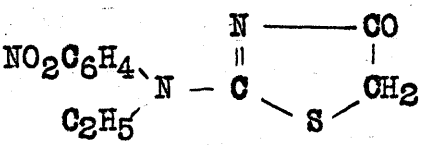
Two grams of this product, 20 cc of alcohol, and 22 cc of concentrated HCl-solution were digested for 20 hours. There was no solid to filter off. On slight dilution with water there developed a cloudiness but no precipitate. On further dilution a yellowish precipitate formed in the acid solution.

Melting point of this solid, 97-98°.

Mixed melting point, 97-98°.

The filtrate, rendered alkaline, yields only a trace of yellow solid.

The formula, therefore, for isomer (B) may be written:



No attempt to hydrolyze isomer (C) was made, primarily because of its limited amount, and secondarily, for the theoretical reason that obtaining probable products of hydrolysis, namely the two primary amines, ethylamine and p-nitroaniline would not serve to fix their relative positions in the thiohydantoin molecule. If a sufficient supply of the isomers could be prepared, and these converted into the respective benzal derivatives, it might be possible to establish the relative positions of the substituting groups in (B) and (C) owing to the fact that the ring in such derivatives has been shown by Dains and his workers to be more resistant to hydrolytic influences than in the unsubstituted compounds. The ethyl- and p-nitrophenyl-mustard-oil glycolides, could probably be isolated and the position of these groups in the respective thiohydantoins inferred. Thus, 3-Ethyl-3-p-nitrophenyl-thiohydantoin on hydrolysis should yield 3-p-nitrophenyl mustard-oil glycolide while the 2-p-nitrophenyl-3-ethyl

isomer should give 3-ethyl mustard-oil glycolide. Such an investigation is contemplated.

12. P-NITROPHENYLBENZYLTHIOHYDANTOIN.

p-nitrophenylthiohydantoin sodium hydroxide,	10 g.
Benzylchloride,	5 cc.
Alcohol,	35 cc.

This mixture was refluxed for 17 hours. Some solid, probably NaCl, was found in the bottom of the flask. On distilling with steam, a brown oil remained, from which the aqueous layer was decanted. The oil was dissolved in hot alcohol. On gradual dilution with water a yellow colloidal suspension formed, from which separated on agitation a dark-brown oil. On further dilution and cooling, a yellow crystalline solid separated. On making a melting point determination, part of the solid appeared to melt at about 121-123° while some of it remained solid above 200°. It may be a mixture of isomers.

NITROGEN DETERMINATION.

Sample,	0.3709 g.
Acid, (.20196 N)	28.20 cc.
Base, "	17.40 cc.
Control, N/5	0.40 cc.
N_2, found,	12.76 percent.
Calculated for ($C_{16}H_{13}O_3N_3S$)	12.84 "

13. HYDROLYSIS OF P-NITROPHENYLBENZYLTHIOHYDANTOIN.

Six grams of the thiohydantoin and 50 cc of concentrated HCl-solution were refluxed for 14½ hours. During digestion, an oil, heavier than the solution, separated.

On decanting the aqueous layer and cooling it a yellow solid separated, increasing in amount on dilution. Melting point 130°. The residue in the flask was extracted with hot concentrated HCl and the solution poured into a beaker and cooled. A mush of light-yellow crystals formed. On steam distilling the strongly acid mixture, no solid comes over. On making the mixture alkaline with soda-ash, and again distilling, no solid came over. The yellow solid melted at 144-145°. Mixed with some p-nitroaniline the melting point was reduced to 115+°.

NITROGEN DETERMINATION ON THE 144-145-DEGREE PRODUCT.

Sample,	0.2227 g.
Acid, (.20196 N)	25.60 cc.
Base, "	15.45 cc.
Control, N/5	0.50 cc.
N_2, found,	12.26 percent
Calculated for $(C_{13}H_{12}O_2N_2)$	12.28 "
$(NO_2C_6H_4 - NH - CH_2C_6H_5)$	

NITROGEN DETERMINATION ON THE 130-DEGREE PRODUCT.

Sample,	0.3219 g.
Acid, (.20196 N)	25.40 cc.
Base, "	12.60 cc.
Control, N/5	0.50 cc.
N_2, found,	10.80 %
Calculated for $NO_2C_6H_4$-N(—CO)(O=C—S—CH_2)	11.77 %

The results indicate that there is at least present in the thiohydantoin preparation, 2-benzyl-2-p-nitroanimo thiohydantoin, $NO_2C_6H_4$-N($C_6H_5CH_2$)-C(=N—)(—CO—CH_2—S—).

IV. EXPERIMENTS WITH NITROTOLUIDINE DERIVATIVES.

$CH_3 - C_6H_3 - NH_2 - NO_2$

(1) (4) (3)

1. CHLORACET-P-TOLUIDIDE.

This compound was prepared in quantity from p-toluidine and chloracetylchloride in the presence of pyridine and acetone by the usual procedure.

2. CHLORACETNITROTOLUIDIDE (1 : 4 : 3).

($CH_3 - C_6H_3 - NO_2 - NH \cdot CO \cdot CH_2Cl$)

Chloracet-p-toluidide was covered with five parts by weight of nitric acid (1.42). On shaking, solution took place with some evolution of heat and escape of brown fumes. After a short time the mixture was poured into water and the solid which separated filtered off. Melting point from strong alcohol, 118°. (Beckurts and Frerichs, 119°).

3. THIOCYANACETNITROTOLUIDIDE (1 : 4 : 3).

Chloracetnitrotoluidide (1:4:3).	50 gms.
Potassium Thiodyanate,	35 gms.
Alcohol,	125 cc.

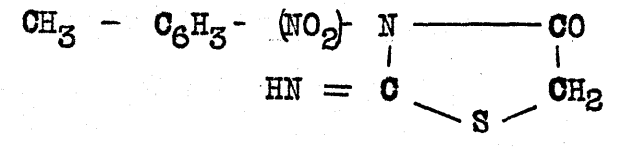
This mixture was refluxed for 30 minutes. On pouring into water a thick heavy oil separated. On cooling, yellow crystals form a fringe on the oil, gradually increase in quantity until the whole mass sets. This should be the 133-degree melting product of Beckurts and Frerichs.

$(CH_3 - C_6H_3 - NO_2 - NH \cdot CO \cdot CH_2 \cdot SCN)$.

4. NITROTOLYLTHIOHYDANTOIN (1:4:3).

The thiocyanacetnitrotoluidide was digested with 1500 cc of water for two-hour# periods, the water being changed twice. On filtering, hot, the filtrate on cooling, deposited a yellow solid, melting at 182+°. (Beckurts and Frerichs, 185°). Yield, 10 grams. A large proportion of the material never went into solution, apparently, but, nevertheless, was converted largely into the thiohydantoin

a mixture of it with the yellow product melting at 175-°. Beckurts and Frerichs represent the compound by the following structural formula,



5. THE NaOH-COMPOUND.

This was prepared by dissolving the thiohydantoin in an equivalent of warm 5% NaOH-solution. On cooling, the salt crystallizes out, is filtered off and carefully dried. Beckurts and Frerichs report it as crystallizing with three moles of water.

6. ETHYL-NITROTOLYLTHIOHYDANTOIN (1:4:3).

Nitrotolylthiohydantoin, NaOH	10 gms.
Ethyl Iodide,	10 gms.
Alcohol,	50 cc.

This mixture was refluxed for several hours, after which it was steam-distilled, A heavy black oil was produced. Separated, washed and dried it is a thick, sticky flowing oil. It was described by Beckurts and Frerichs as "a light-brown thickly flowing oil."

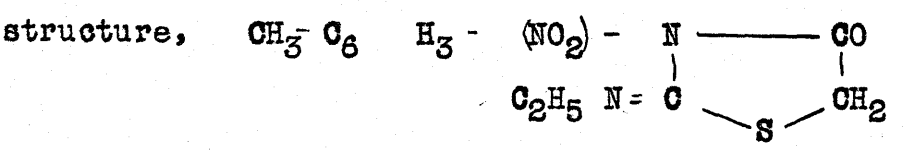
NITROGEN DETERMINATION.

Sample,	0.3684 g.
Acid, N/5	41.75 cc.
Base, "	21.65 cc.
Control,"	0.41 cc.

N_2, found, 14.97 percent

Calculated for ($C_{12}H_{13}O_3N_3S$) 15.06 "

Beckurts and Frerichs assume for it the structure,



7. HYDROLYSIS OF ETHYL NITROTOLYLTHIOHYDANTOIN (1:4:3)

The thiohydantoin was refluxed with concentrated HCl and alcohol (8 parts) for 11 hours. The acid mixture on steam distilling yields a yellow distillate indicating the presence of a weak base, probably the secondary amine. An oil separates in the flask during distillation. The distillate continued to come over yellow after a liter of it had collected. The distillation was stopped at this point and the oil in the flask examined. It was washed with water, the washings added to the acid solution obtained by decantation from the oil, and the whole made alkaline with soda-ash. A yellow solid formed, probably identical with the material coloring the distillate. The black, washed residue in the distilling flask solidified on standing and cooling.

Melting point of the yellow solid, 65°

Reported in the literature, 58-59°

NITROGEN DETERMINATION ON THE 65-DEGREE PRODUCT.

Sample, 0.4000 gms.

Acid, N/5	40.10 cc.
Base, "	15.90 cc.
Controh,"	0.41 cc.
N_2, found,	16.65 percent.
Calculated for ($C_9H_{12}O_2N_2$)	15.56 "

NITROGEN DETERMINATION ON THE RESIDUE.

Sample,	0.4548 g.
Acid, N/5	40.30 cc.
Base, "	17.20 cc.
Control,"	0.41 cc.
N_2, found,	~~30.97~~ 14.41 percent.
Calculated for ($C_{10}H_8O_4N_2S$)	11.11 "

The results of analysis of these hydrolytic products leads nowhere except to suggest that the disubstituted thiohydantoin preparation may have been a mixture of isomers.

The above 65-degree product was now suspected of being a mixture of the secondary amine with some nitrotoluidine. Advantage was taken of the difference in basicity of these two substances. By dissolving the product in hot concentrated HCl and pouring the solution into water the hydrochloride of the secondary amine is decomposed while the other salt remains in solution. The product was subjected to this method of purification and a nitrogen determination again made.

NITROGEN DETERMINATION.

Sample,	0.2292 gms.
Acid, N/5	26.90 cc.
Base, "	13.87 cc.
Control,"	0.55 cc.
N_2, found,	15.24 percent.
Calculated for ($C_9H_{12}O_2N_2$)	15.56 "

This supports the conclusion that a mixture of isomerides was obtained in the ethyl-nitrotolyl-thiohydantoin preparation.

The whole series of preparations was now repeated.

The SCN-derivative, 33 grams, was heated with 2200 cc of water for two hours. The product, at first oily in the hot water, gradaally solidified as boiling continued. The filtrate deposited a bright-yellow crystalline solid. The residue was dark in color but crystalline in structure.

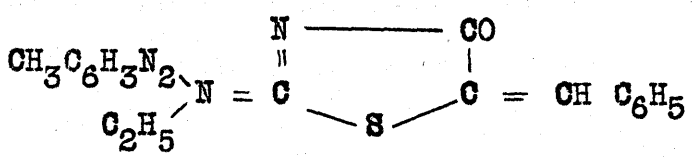
Ten grams of the product were converted into the NaOH-salt by warming them to complete solution in an equivalent of 5% NaOH and cooling. A mass of crystals separated from a nearly black solution. Nine grams of the salt were obtained. A further preparation amounted to 15 gms.

Nine grams of the salt, 4.2 grams of ethyl iodide, and 13 cc of alcohol (from lime) were heated in a closed tube in steam for 30 minutes. The tube contents were transferred to a distilling flask and subjected to steam distillation. The

familiar dark-colored product appeared. On cooling it became almost too thick to flow. Washed several times with hot water, the product came out as a chocolate-colored, thick mass, almost brittle at 0^{o}. This product was taken to be the ethyl-nitrotolylthiohydantoin.

9. ETHYL NITROTOLYLBENZALTHIOHYDANTOIN.

Ethylnitrotolylthiohydantoin, 6.2 grams, and benzaldehyde, 5 grams, were dissolved in alcohol and a few cc of 5% NaOH added. By scratching the sides of the container with a glass rod, fine crystals soon began to appear, light-brown in color. Washed with alcohol and ether separately, three grams of the product were obtained, melting at $155-156^{o}$. The product, which was assumed to be



was examined for nitrogen content.

NITROGEN DETERMINATION.

Sample,	0.3379,	0.3356 g.
Acid, N/5	27.89,	29.86 cc.
Base, "	14.27,	16.24 cc.
Control,"	0.55,	0.55 cc.
N_2, found,	10.83,	11.07 %
Calculated for $(C_{19}H_{17}O_3N_3S)$,		11.44 "

10. ATTEMPT TO HYDROLIZE THE BENZAL COMPOUND.

A gram of the benzal derivative was heated with a solution containing 20 cc of concentrated HCl and 10 cc of alcohol, for 3 to 4 hours. The undissolved greenish-yellow powder was filtered off and found to melt at 172°. Mixed with some of the product used the melting point was 170°. The filtrate, made alkaline with soda-ash and steam-distilled gave a reddish-colored distillate but no solid separated from it. Extracted with ether it yielded a small portion of a product melting roughly at 100 degrees and hence could not have been the pure secondary amine. It may have been, however, a mixture containing this product and some nitrotoluidine, but this assumption could not be verified on account of the limited quantity of material. Further work as follows gave favorable results.

11. ETHYLNITROTOLYLTHIOHYDANTOIN (1:4:3).

NaOH-salt 15 gms.

Ethyl Iodide, 7 gms.

This mixture was refluxed in alcohol for 16 hours. A sticky dark-red product was obtained.

12. ETHYLNITROTOLYLBENZALTHIOHYDANTOIN (1:4:3).

Ethylnitrotolylthiohydantoin, 3 gms,

Benzaldehyde, 1 gm#.

This mixture in alcohol containing a little NaOH solution, on standing yielded a product which, after thorough digestion with ether, melted at 178°.

Another preparation gave enough of the product for analysis and hydrolysis.

NITROGEN DETERMINATION.

Sample,	0.2110 gms.
Acid, (.20196 N)	23.10 cc.
Base, "	14.60 cc.
Control, N/5	0. 50 cc.
N_2, found,	10.72 %
Calculated for ($C_{19}H_{17}O_3N_3S$)	11.44 %

The product on standing in a vacuum dessicator over sulphuric acid for 12 hours afforded the following analysis:

Sample,	0.2271 gms.
Acid, (.20196 N)	26.70 cc.
Base, "	17.00 cc.
Control, N/5	0.50 cc.
N_2, found,	11.46 %
Calculated for ($C_{19}H_{17}O_3N_3S$)	11.44 %

13. HYDROLYSIS OF THE BENZAL COMPOUND.

Benzal compound,	2 gms.
Conc. HCl	20 cc.
Alcohol, (95%)	20 cc.

This mixture was digested for 10 hours. Some

of the solid removed, melted at 172-175°. Mixed with original product, melted at 176-176.5° .

The time of digestion was now continued for 21 hours longer.

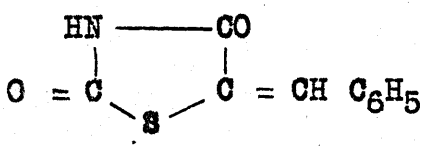
The mixture was filtered. The residue melted at 176-177°, the original benzal compound at 176-178° and a mixture of the two at 174-177°. The recovered unchanged product weighed 1.265 grams. This meant that only about 37% of the product, if any, had undergone change, in the 31 hours-period of digestion.

The filtrate on dilution with water yielded a pale yellow precipitate melting near 90°. Further dilution afforded more of the solid melting at 83-91°. The filtrate from this being rather highly colored, it was extracted with ether which gave a residue melting at 103-114°. (Probably a mixture of the primary (m.p. 109) and secondary (m.p. 58-59°) amines.) Some of this residue gave a positive carbamine reaction. The remainder of the residue was dissolved in concentrated HCl and the solution diluted. Cloudiness developed but no solid settled out. Rendered short of neutral with $Na_2 CO_3$ a yellow solid (changing to red) separated from the slightly acid solution. On making the solution alkaline there was no further precipitation. On drying, the solid was of an orange color and melted at 113-114°. Mixed with nitrotolyluidine (1:4:3),

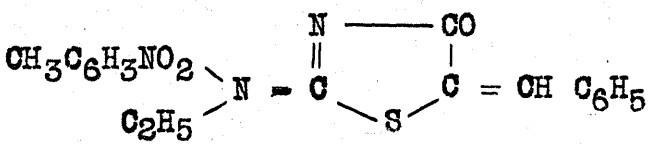
113-114°. This product was therefore the primary amine.

Analysis of the product melting in the neighborhood of 90° showed the following results:

Sample,	0.2015 gms.
Acid, (.20196 N)	24.00 cc.
Base, "	18.40 cc.
Control, N/5	0.50 cc.
N_2, found,	7.08 %
Calculated for ($C_{10}H_6O_2NS$)	6.86 %



The results are explainable on the assumption of a mixture of the isomeric substances,



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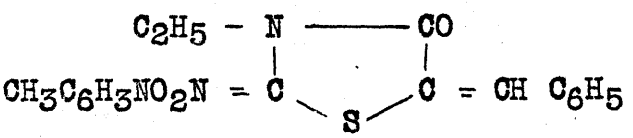

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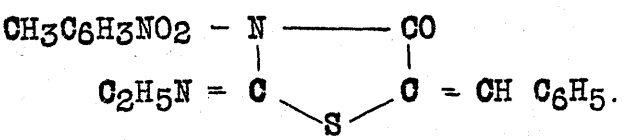
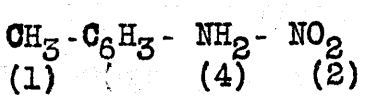
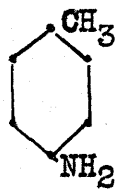


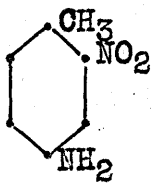
V. EXPERIMENTS WITH NITROTOLUIDINE DERIVATIVES.



1. The supply of nitrotoluidine (1:4:2) was prepared by the following method taken from the thesis of H. J. Long.

"Twenty grams of para toluidine was cooled in a beaker with four hundred grams of concentrated sulfuric acid to a temperature of zero degrees. This was stirred while a mixture of fifteen grams of fuming nitric acid and sixty grams of sulfuric acid was slowly added. The mixture was poured on to ice and diluted to three or four liters and the acid neutralized with sodium carbonate. This left a heavy scum of the nitro toluidine which was filtered off and recrystallized by extracting with hot dilute hydrochloric acid and precipitating with sodium carbonate or ammonia. It was in light yellow crystals whose melting point was 78-79 degrees."





2. CHLORACETNITROTOLUIDIDE (1:4:2).

Nitrotoluidine,	15 gms.
Chloracetylchloride,	8 cc.
Pyridine,	8 cc.
Acetone,	65 cc.

The preparation was made in the usual manner. A brown solid separated on dilution of the reaction mixture. Yield 23 grams, or one hundred

percent. A number of these preparations was made to insure sufficient material for work. From dilute alcohol, melting point 122-123° (Beckurts and Frerichs, 129°).

3. THIOCYANACETNITROTOLUIDE (1:4:2).

Chloracetnitrotoluidide,	65 gms.
Potassium Thiocyanate,	45 gms.
Alcohol,	200 cc.

The mixture was refluxed for 30 minutes. The HCl began to form rather suddenly after 10 minutes of heating. Some of the alcohol was removed from the filtrate by distillation, and the residue poured into ice-water. A thick gummy brown mass collected on the stirring rod, melting point from alcohol 167-°. This was considered to be the product of Beckurts and Frerichs melting at 184° (from alcohol).

4. NITROTOLYLTHIOHYCANTOIN (1:4:2).

The product obtained in (3) was digested in two liters of water for about four hours. The yield of thiohydantoin was 49 grams. From dilute alcohol it melted at 196-197°. It was considered to be the product of Beckurts and Frerichs melting from alcohol, at 206-207°.

5. THE NaOH SALT.

Nitrotolylthiohydantoin (1:4:2),	49 gms.
NaOH, (1.44 N),	137 cc.

This mixture was warmed to partial solution and cooled. A bright orange-colored solid crystallized out. According to Beckurts and Frerichs it contains two moles of water of crystallization.

6. ETHYLNITROTOLYLTHIOHYDANTOIN (1:4:2).

NaOH-salt,	10 gms.
Ethyl Iodide,	3 cc.
Alcohol,	22 cc.
[illegible],	
Time of digestion,	7 hours.

On steam distilling, a heavy oily residue was obtained. This was dissolved in alcohol and the solution cautiously diluted with water. A black tarry substance separating at first was filtered off. The filtrate, on further dilution, yielded a bright yellow precipitate, described by Beckurts and Frerichs as "yellow leaflets, m. p. 142°".

NITROGEN DETERMINATION.

Sample,	0.3166 gms.
Acid, N/5	35.97 cc.
Base, "	18.23 cc.
Control,"	0.55 cc.

N_2, found,	15.23 %
Calculated for ($C_{12}H_{13}O_3N_3S$)	15.06 %

7. HYDROLYSIS OF ETHYLNITROTOLYLTHIOHYDANTOIN (1:4:2).

The Thiohydantoin,	5 gms.
Hydrochloric Acid (25%),	40 cc.
Time of digestion,	7¼ hrs.

On distilling with steam, no oil or solid came over from the acid solution. Made alkaline, an orange-colored solid separated. Again steam-distilled, the distillate came over yellowish in color. On standing a little, orange-colored solid separated. An ether extract yielded needles of the substance. This product melts above 50°. (Accepted for the secondary amine, 49°).

The assumption that here was a mixture possibly of the secondary amine with some nitro-toluidine was partially confirmed on analysis of the product.

NITROGEN DETERMINATION.

Sample,	0.3435 gms
Acid, N/5	27.59 cc.
Base, "	5.89 cc.
Control,"	0.55 cc.
N_2, found,	17.44 %
Calculated for, ($CH_3C_6H_3 \cdot NO_2NH \cdot C_2H_5$)	15.56 %
Calculated for, ($CH_3C_5H_3 \cdot NO_2 - NH_2$)	18.40 %

The suspicion of isomers led to further preparations with special attention to the formation of the NaOH-salt, the ethyl derivative and to the hydrolytic products of the latter. The experiments immediatd y following cover this work.

8. NITROTOLYLTHIOHYDANTOIN (1:4:2).

Twenty-eight grams of this product melting at 202° were obtained. (Beckurts and Frerichs, 206-207°).

9. NITROTOLYLTHIOHYDANTOIN SODIUM HYDROXIDE (1:4:2).

The thiohydantoin,	28 gms.
Sodium hydroxide, (1.44 N),	78.1 cc.

This mixture was warmed to nearly complete solution, the solution cooled and the solid which separated, filtered off. The blood-red filtrate on acidifying gave a heavy white precipitate. (Not the original thiohydantoin).

On treating some of the salt with water, it dissolved. On rendering this solution acid with acetic acid, a white precipitate formed, melting at 195-197°. Mixed with some of the thiohydantoin, it melted at 191-192°. This result was taken to mean that the Na OH-compound prepared was practically free from impurities.

10. ETHYLNITROTOLYLTHIOHYDANTOIN (1:4:2).

NaOH-Compound,	10 gms.
Ethyl Iodide,	4 cc.
Alcohol,	35 cc.

This mixture was refluxed for 12 hours. From this reaction mixture a brown solid melting at 140°, was obtained. This should be the product of Beckurts and Frerichs melting at 142°, and may be considered to be in a fairly pure state.

NITROGEN DETERMINATION.

Sample,	0.3117,	0.3584 gms.
Acid, (.20196 N)	30.00,	22.20 cc.
Base, "	11.30,	1.40 cc.
Control, N/5	0.55,	0.55 cc.
N_2, found,	16.47,	16.13 %
Calculated for ($C_{12}H_{13}O_3N_3S$)		15.06 %

Evidently the product was not the pure ethyl derivative.

11. HYDROLYSIS OF PREPARATION (10).

Three grams were refluxed with 25 cc of conc. HCl, with the addition of a little alcohol, for 11½ hours. Filtering left only a trace of residue. The filtrate with ammonia formed a yellow precipitate which, recovered by means of ether, yields an oil.

NITROGEN DETERMINATION.

Sample,	0.3051,	0.3313 gms.
Acid, (.20196 N)	28.10,	28.70 cc.

Base, (.20196 N)	9.70,	8.50 cc.
Control, N/5	0.55,	0.55 cc.
N_2, found,	16.59,	16.78 %
Calculated for ($C_9H_{12}O_2N_2$)		15.56 %

It is here again evident that the pure secondary amine was not secured.

These results might be accounted for on the theory that some of the free thiohydantoin was present in the NaOH-preparation which, carried along and hydrolyzed, would yield some nitrotoluidine. This, mixed with the secondary amine would on analysis give high results for nitrogen.

In this connection it should be noted that in preparing the NaOH-salt, the filtrate acidified with acetic acid gave a product which from hot dilute alcohol precipitated as a brown solid melting near 173°. A light-yellow product melting at 114° was also obtained from this source. Contamination of the NaOH-salt may have resulted from these sources.

12. NITROTOLYLETHYLTHIOHYDANTOIN (1:4:2).

In this case ten grams of the sodium hydroxide compound, 5 cc of ethyl iodide and 31 cc of alcohol were refluxed for 14½ hours. A black oil, with a tendency to formation of yellow crystals, was obtained.

13. HYDROLYSIS OF PRODUCT FROM (12).

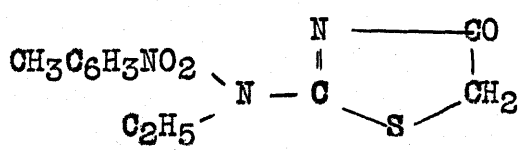
The above product was dissolved in some alcohol and refluxed with 80 cc of concentrated HCl for 13 hours.

From this reaction mixture on rendering it nearly alkaline with ammonia, a reddish-brown flocculent precipitate was secured. This was taken up with ether and dried over $CaCl_2$. A dark-red oil was obtained from the ether extract. This was dried at 110° and analyzed.

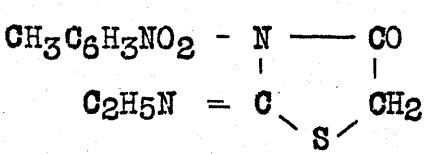
NITROGEN DETERMINATION.

Sample,	0.3249,	0.3153 gms.
Acid, (.20196 N)	28.40,	25.20 cc.
Base, "	9.55,	7.20 cc.
Control, N/5	0.50,	0.50 cc.
N_2, found,	15.94,	15.70 %
Calculated for ($C_9H_{12}O_2N_2$)		15.56 %

As a result of this series of experiments, one may conclude that the ethyl nitrotolylthiohydantoin preparations contained the product,



possibly, in some cases, mixed with one, or the other, or both, of the possibly isomers,



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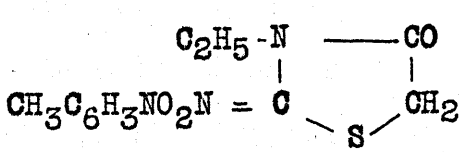


14. NITROTOLYLBENZYLTHIOHYDANTOIN (1:4:2).

NaOH-salt,	10 gms.
Benzylchloride,	6 cc.
Alcohol,	30 cc.
Time of digestion,	14 hours.

The resulting product was steam-distilled to remove alcohol and excess benzylchloride, and then poured into water. A heavy black, sticky oil was obtained. After extraction with ether it was dried at 110°.

NITROGEN DETERMINATION.

Sample,	0.3293 gms.
Acid, N/5	24.30 cc.
Base, "	10.70 cc.
Control,"	0.55 cc.
N_2, found,	11.09 %
Calculated for ($C_{17}H_{15}O_3N_3S$)	12.32 %

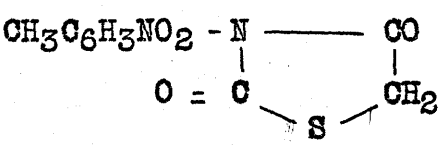
15. ATTEMPT TO HYDROLYZE NITROTOLYLBENZYLTHIOHYDANTOIN, (1:4:2)

Nitrotolylbenzylthiohydantoin,	13 gms.
Conc. HCl,	100 cc.
Alcohol,	25 cc.
Time of digestion,	14 hours.

The reaction-mixture was filtered while still fairly hot. The residue consisted of peculiar pebble-like aggregates, varying in color from brown to black, and melting at 178-179°. The filtrate on

cooling deposited fine flakes melting near 165°. On rendering the filtrate alkaline with soda-ash a negligable quantity of a brown material separated. The pellets from dilute alcohol gave an orange-colored suspension. The pellets appear to be the main product of the reaction. They do not steam-distill, appearing to liquify in the flask. Made alkaline and steam-distilled, they are converted into a black non-volatile oil. This result suggests that the pellets may have been the HCl-salt possibly of the secondary amine. A nitrogen determination was resorted to in order to help decide the matter.

Sample,	0.3292 gms.
Acid (.2038 N)	28.20 cc.
Base, "	15.20 cc.
Control, N/5	0.55 cc.
N_2, found,	10.80 %
Calculated for ($C_{14}H_{14}O_2N_2$)	12.61 %
Calculated for ($C_{10}H_8O_4N_2S$)	11.11 %



No definite conclusions can be drawn from the results with the benzyl derivatives.

VI. EXPERIMENTS WITH NITROTOLUIDINE DERIVATIVES.

CH_3 C_6H_3 NO_2 NO_2
(1) (2) (5)

1. ACET-O-TOLUIDIDE.

O-Toluidine,	100 gms.
Acetic Anhydride,	20 cc.
Glacial Acetic Acid,	83 cc.

The above mixture was refluxed for 10½ hours. On pouring the reaction mixture into water a nearly colorless solid separated, and was considered sufficiently pure for use after washing free from acid.

2. NITROTOLUIDIDE (1:2:5).

The following procedure taken from the thesis of H. J. Long was used for the preparation of this compound, however without very gratifying results.

"In a bath kept at 30 to 35 degrees, 60 grams of acet-o-toluidide were slowly added to a mixture of 92 cc fuming HNO_3 and 116 cc of ordinary HNO_3. After the reaction quieted down the mixture was allowed to stand over night. It was the poured into ice-water with rapid stirring, filtered, and washed thoroughly with water. It may be dried or hydrolyzed in the wet state. For hydrolysis, it was refluxed for two to three hours with four or

five times its weight of 25% hydrochloric acid.

The acid mixture was then subjected to steam distillation. The 3-nitro compound being a weak base, its salt is decomposed by water and will steam distill, leaving the 5-nitro compound in the flask.

It was found from experience that about 15 liters of distillate must be collected to insure recovery of all the 3-nitro compound.

The 5-nitro compound usually came down as yellow crystals on cooling the residual solution.

After about three weeks time and by the use of over 200 grams of the acet-o-toluidide, 18 grams of the 5-nitro compound melting at 130° was secured. This was used in the experiments which follow.

3. CHLORACETNITROTOLUIDIDE (1:2:5).

Nitrotoluidide, (1:2:5),	18.1 gms.
Chloracetylchloride,	9 cc.
Pyridine,	12 cc.
Acetone,	80 cc.

The chloracetylchloride, dissolved in some acetone, was added slowly to the cooled and stirred acetone solution of the other ingredients. On pouring the reaction-mixture into water, an oil first separated, but soon changed to a yellowish-brown solid, melting, from alcohol,

at 115-116°. (Beckurts and Frerichs, 122°).
Yield, 27 grams, or 100 percent.

4. THIOCYANACETNITROTOLUIDIDE, (1:2:5).

Chloracetnitrotoluidide,	24 gms.
Potassium Thiocyanate,	17, gms.
Alcohol,	50 cc.
Time of digestion,	30 min.

Complete solution of all materials apparently took place at first, followed in ten minutes by the separation of KCl. The latter was filtered off and washed with alcohol. Filtrate and washings were poured into a large volume of ice-water. A yellow, curdy precipitate formed collecting on the stirring rod in a soft, clinging rubbery mass. A portion of this was allowed to stand in contact with water until after several days it had changed to a yellow solid melting at 166-167°. (Beckurts and Frerichs describe their thiohydantoin at 172°. They state that they found "no evidence of an iso-compound" and apparently did not encounter the rubbery mass alluded to above).

The rubbery mass may be molded with the hands like gum. From alcohol it is recovered apparently unchanged. Some of it from glacial acetic acid is obtaiad as a solid melting near 165°. Some of it, digested in 1½ liters of boiling water, yields a

yellowish solid. Some digested in boiling alcohol, yields a solution which on dilution gives a yellow precipitate, slowly collecting.

The original wash-liquid decanted from the product on standing overnight deposited some solid, melting at 154-155°. This may have been some of the S CN-derivative described by Beckurts and Frerichs as melting at 158°.

Repeated digestion of the product, first in a large volume of water and finally in glacial acetic acid, resulted in its conversion to the thiohydantoin melting at 169-173°. (Beckurts and Frerichs, 172°).

Yield of thiohydantoin, 11.83 grams.

5. NITROTOLYLTHIOHYDANTOIN SODIUM HYDROXIDE (1:2:5).

Nitrotolylthiohydantoin (1:2:5), 11.8 gms.
NaOH-solution (1.44N), 33 cc.

This mixture was warmed to nearly complete solution, the liquid decanted and the residue with more alkali warmed to complete solution. On cooling, a yellow crystalline solid and a blood-red filtrate were obtained. The latter with acetic acid yielded 2-3 grams of solid, not the thiohydantoin.

Ten grams of the dry sodium hydroxide salt were obtained. It is described by Beckurts and Frerichs as crystallizing with three moles of water.

6. ETHYLNITROTOLYLTHIOHYDANTOIN (1:2:5).

Nitrotolylthiohydantoin, 10 grams.

Ethyl Iodide, 4 cc.

This mixture was digested in alcohol for eighteen hours. On standing over night a crystalline solid (A) had formed in the bottom of the flask. This was removed and washed with water to remove any mineral salt (Na Cl) which might be mixed with it, and carefully dried. It melted then at 125-126°. From ether, however, it melted well at 128-129°. (Beckurts and Frerichs, 127-128°).

The filtrate from (A) on dilution yielded a heavy chocolate-colored semisolid. This was dissolved in alcohol and the solution diluted with water. A yellow, more or less crystalline solid (B) with a strong adhesive tendency separated. A melting point attempt resulted in a gradual change extending from 130° up to and beyond 150°.

Mixed with some of the 128-129-degree product (A) the melting point was reduced to 110-115°. It seemed from this that they were not identical. Slightly less than three grams of (A) were obtained. This was reserved for analysis and hydrolysis. The higher melting mixture (B) on washing with ether melted well at 179-180°.

Evidently two substances have been isolated on the basis of their difference in solubility in ether.

NITROGEN DETERMINATION ON SUBSTANCE (A).

Sample,	0.2740 gms.
Acid, (.20196 N)	25.60 cc.
Base, "	10.65 cc.
Control, N/5	0.50 cc.
N_2, found,	14.92 %
Calculated for ($C_{12}H_{13}O_3N_3S$)	15.05 %

NITROGEN DETERMINATION ON SUBSTANCE (B).

Sample,	0.2457 gms.
Acid, (.20196 N)	23.20 cc.
Base, "	9.75 cc.
Control, N/5	0.50 cc.
N_2, found,	14.91 %
Calculated for ($C_{12}H_{13}O_3N_3S$)	15.05 %

Substances (A) and (B) therefore have the same nitrogen content.

7. HYDROLYSIS OF SUBSTANCE (A).

Substance (A),	2.5 grams.
Concentrated HCl,	25 cc.

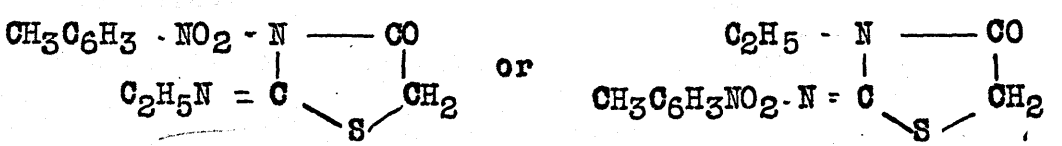
(A) was dissolved in a little hot alcohol and the HCl added. The digestion was carried over a period of 13 hours. On filtering the acid solution only, a few black granules were left as a residue. On diluting the filtrate with water, a yellow crystalline solid separated from the acid solution. This melted at 132-132.5°.

The filtrate from this on adding alkali short of neutrality yielded a further supply of yellow shining crystals melting sharply at 131.5°. The filtrate from this second crop on rendering alkaline with NaOH and warming gave off an alkaline (to litmus) gas. The second filtrate obtained above was evaporated on the water-bath to practical dryness. The residue was transferred to a distilling flask, made alkaline and distilled. An alkaline distillate was secured which gave the carbamine reaction, thus indicating the presence of a volatile primary amine ($C_2H_5NH_2$). This suggested that substance (A) was an α,β-substituted product. Analysis of the hydrolytic product obtained confirmed this conclusion.

NITROGEN DETERMINATION ON THE 131.5-DEGREE PRODUCT.

Sample,	0.2239 gms.
Acid, (.20196 N)	25.00 cc.
Base, "	9.90 cc.
Control, N/5	0.50 cc.
N_2, found,	18.44 %
Calculated for ($C_7H_8O_2N_2$)	18.42 %
(CH_3 C_6H_3 NO_2 NH_2)	

In view of these results one of the following structures may be assigned to product (A).



Beckurts and Frerichs assigned the first to their product.

8. HYDROLYSIS OF SUBSTANCE (B).

Substance (B),	2.0 gms.
Conc. HCl,	20 cc.
Alcohol,	10 cc.
Time of digestion,	14 hours.

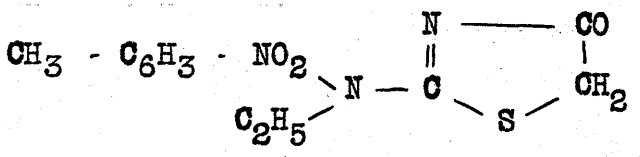
The reaction-mixture on cooling showed no evidence of solid formation, at first. On further standing there was evidence of some yellow crystal-formation. The contents of the flask were transferred to a beaker, the flask being rinsed out first with dilute alcohol and finally with water. On adding the washings to the main solution a yellow solid immediately separated from the acid medium. Melting point, 98-99°, sharp. Reported in the literature 98°, for the secondary amine. This product was dried in a vacuum dessicator over sulphuric acid.

NITROGEN DETERMINATION ON THE 98-DEGREE PRODUCT.

Sample,	0.2058 gms.
Acid, (.20196 N)	23.10 cc.
Base, "	11.55 cc.
Control, N/5	0.50 cc.
N_2, found,	15.22 %
Calculated for $(C_9H_{12}O_2N_2)$	15.56 %

$-(CH_3 \cdot C_6H_3 \cdot NO_2 \cdot OH \cdot C_2H_5)$

Structure for substance (B).



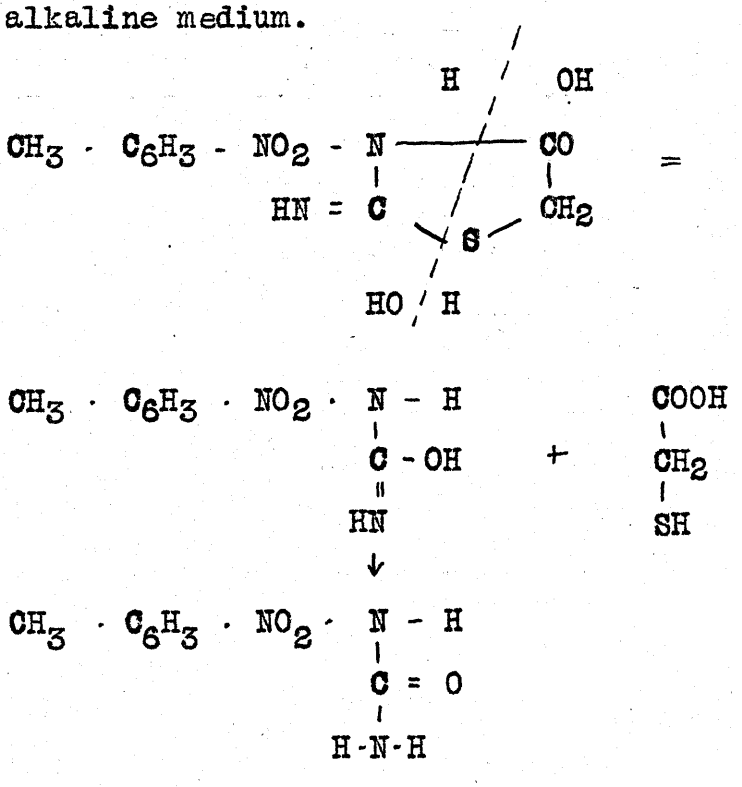
In all cases where the sodium hydroxide salt of a thiohydantoin was prepared it had been noticed that the filtrate was always highly colored and that on rendering it acid with acetic acid a light colored or colorless product was obtained which did not melt sharply and did not agree with that for the thiohydantoin which one might expect to recover under such conditions.

In order to investigate this problem, the precipitate obtained on acidifying filtrate from the sodium hydroxide nitrotolylthiohydantoin, was digested in ether. A partial separation, at least, into two parts was effected, melting in the neighborhood of 120 and 130°. The higher melting product was analyzed for nitrogen with the results following:

Sample,	0.2544 gms.
Acid, (.20196 N)	25.45 cc.
Base, "	6.85 cc.
Control N/5,	0.50 cc.
N_2, found,	20.18 %.

The following reaction suggested itself as a possibly explanation of what may have occurred

in the alkaline medium.



$(C_8H_9O_3N_3)$.

N_2 = 21.53 percent.

REFERENCE INDEX

I wish here to express my appreciation of the sympathetic cooperation of Dr.F. B. Dains during the prosecution of this work.